Social Chemistry and Toxic Chemicals: Assessing the Likelihood for Increased Regulation of BPA in the United States

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Daniel Latham

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Adviser: Sheldon Krimsky

Abstract

Bisphenol A (BPA), a chemical used in the formulation of many plastic products, has recently become a matter of public concern due to its association with detrimental effects on human development at doses that individuals are exposed to on a daily basis. This research examines the recent scientific discoveries, ethical issues, stakeholder groups and the decisions of other nations to determine the likelihood of the United States setting federal regulation restricting the use of BPA in consumer products. While the science does not offer a clear solution and the majority of the international community believes that BPA is safe for unrestricted use, the ethical arguments and trends of state and local governments suggest that the federal government will likely put forth restrictions on the sale of BPA-containing products made for infants.

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Chapter 1: Introduction

Bisphenol A (BPA), a chemical used in the formulation of many plastic products, has recently come into public concern due to its association with detrimental effects on human development at doses that individuals are exposed to on a daily basis. BPA is used in the formulation of common plastics, most notably polycarbonates and epoxy resins. These plastics are in turn used in a multitude of products, such as food and beverage containers, dental sealants, and linings for canned food (vom Saal and Myers, 2008). With such wide usage humans cannot help but be exposed to BPA. Furthermore, it has been determined that humans are regularly exposed to levels of BPA above the maximum tolerable dose mandated by the U.S. Environmental Protection Agency (EPA) (von Saal *et al*, 2007). These exposures occur predominantly through ingestion of food and beverages that contain BPA, which results from the leeching of the monomer from plastics. In response to these concerns, the Food and Drug Administration (FDA) has elected to perform risk assessments of human exposure to BPA. However, as of yet there has been no further federal regulation of the chemical beyond the original exposure thresholds.

Due to consumer pressure certain producers who use BPA have been driven to rethink how they formulate their plastics. Manufacturers of baby bottles and personal water containers in particular have come under fire and have subsequently begun producing BPA-free bottles and containers (Newsday, 2009). However, the U.S. federal government, namely the FDA, has been noticeably hesitant regarding controlling the compound beyond the existing federal standards. Canada has banned its use in the manufacturing of baby bottles and the import of baby bottles containing the chemical. Is

the U.S. government, and by extension, the FDA, waiting for some critical document or event that will decide the issue? Is there conflicting science?

Through perseverance and innovation scientists have created a suite of chemical compounds designed to make life easier. These substances have enabled the human race to progress from a subsistence lifestyle and instead delve into topics that have piqued their natural curiosities. Life-saving medicines have extended the average human life-expectancy and pesticides and fertilizers have allowed for greater crop-yields, which in turn have allowed populations to expand rapidly. However, sometimes these chemicals, though designed to be beneficial, have unintended consequences that are not seen until a great many years later. Dichloro-Diphenyl-Trichloroethane (DDT), polychlorinated biphenyls (PCBs), diethylstilbesterol (DES) -- all are examples of compounds that were at one time thought to be safe and were widely used until environmental and human health issues began cropping up as a result of their use.

Rachel Carson, author of *Silent Spring*, must be given credit for first successfully publicizing the damage that widespread use of chemicals can cause. She argued that the overuse of powerful pesticides, particularly DDT, were having severely detrimental effects on wildlife, and that human beings were just as much at risk (Carson, 1962). Ultimately, her work was largely recognized for its opposition to DDT use in the United States, though its use to combat malaria continues in many developing countries.

Hailed as a successor to Carson, Theo Colborn saw a different pattern of chemical exposure. She identified a more insidious threat in endocrine disrupting chemicals which, while unexpected, affect the ability of wildlife to reproduce and develop correctly. Chemicals once thought to be safe, or perhaps only threatening at very high

concentrations, were discovered to have detrimental effects at concentrations much lower than previously assumed (Colborn *et al*, 1997). Through the work of Colborn and many other concerned scientists, the Environmental Endocrine Hypothesis was postulated. The Hypothesis states, in simplified terms, that humans and other organisms are constantly being bathed in chemicals that can alter our hormones at very low levels of exposure. Due to the low, but constant level of exposure and the complex mechanics of endocrine systems, acute responses to exposure aren't seen. Furthermore, classic chronic responses, such as cancer, have not been observed in wildlife studies. These chemicals are having a wide range of effects, including feminizing species of fish and causing physical abnormalities in developing fetuses. Human data on these effects are limited at best, as there are no longitudinal studies examining the relationships between constant low dose exposures and their potentially adverse effects. The lack of concrete evidence has been contentious among scientists, some questioning the validity of this hypothesis. Its establishment has spurred investigation into the effects of widely used, mass-produced chemicals that were long thought to be safe because there were no acute responses associated with exposure to them. Such is the case of BPA, which came under closer scrutiny in the late 1990s after the discovery was made that BPA was leeching out of plastic laboratory equipment in sensitive experiments (Krimsky, 2000).

The aim of my thesis is to examine the constellation of factors that may determine whether or not federal regulators will change their policy of largely unrestricted use of BPA in commercial products. My thesis focuses on the following questions:

1. What is BPA? What is it used for? Are there any alternatives? Through what consumer products is the public exposed?
2. What has the U.S. government done in the past to limit exposure? What were these standards based on?

3. Is the compound toxic enough to warrant regulation or restriction? What are the regulatory options that exist for control of potentially toxic chemicals?
4. What is the latest science on BPA? Is there considerable dissention muddling the issue?
5. Which government agency or agencies are responsible for investigating and regulating BPA in food contact uses, and what is their current stance?
6. What is the current public debate on BPA? Who are the stakeholders involved, and what kind of influence can they have on regulators?
7. Have other countries approached this problem prior to the United States? If so, what are their determinations? Are there some data that U.S. regulators are missing?
8. Has the U.S. reached a point where it should actively consider regulating BPA, in light of the weight of scientific evidence and public pressure?

Through these questions the issues surrounding BPA will be framed, including a toxicological assessment, an identification of stakeholders, and a discussion of how they interact and drive toxic chemical policy. Society is facing a potentially serious threat, one that has never before been considered. While DDT and PCBs also saw widespread use, the scope of consumer products that contain BPA is staggering. Humans are undoubtedly exposed via contact through containers bearing food, water, and other substances on a daily basis. There has been growing research on the effects of BPA on the environment and aquatic life. We are certain that BPA has been released into the environment at volumes as large as 181,768 pounds per year (NTP-CERHR, 2008). This research will focus on BPA's relationship to human health and the suspected primary route of exposure through food-contact items as well as related items.

Should BPA be adequately regulated, products containing it will have to be reformulated with a safer substitute. Is there a substitute for BPA that costs the same amount of money to produce? These are all important issues which will have to be investigated. My thesis will provide assistance in understanding the rationale for new BPA restrictions being established in the United States.

Methodology

The research for my thesis inquiry consists of a thorough literature review of peer reviewed journals, books, articles, government reports and the print media relating to BPA and its effects on humans, domestic stances towards the chemical and international reactions to BPA.

Chapter Outline

The questions listed above provide a framework for the research I conducted. To begin, Chapter 2 presents a history of bisphenol A and includes documentation concerning its formulation, commercial use, early studies used to set exposure levels, and regulatory actions taken prior to the late 1990s, at which time research on BPA increased. This chapter concludes with discoveries that revealed that BPA might be potentially harmful to humans at very low doses.

Following this, Chapter 3 presents a literature review on the toxicology of BPA, which covers the late 1990s to present day. This review examines research that highlights concern for BPA exposure as well as reports that claim that there is no cause for concern. It also documents current gaps in our understanding of bisphenol A risks, both in measurements of the degree of exposure and the degree of uncertainty surrounding the low-dose effect phenomenon.

Chapter 4 examines the role of the U.S. government in protecting the public from exposure to chemicals that can interact with human physiology at very low concentrations. Because BPA is found in a variety of products, particularly food and

beverage containers, it is important to identify which federal and state agencies would be involved in potential regulatory actions. Two government entities, the Food and Drug Administration (FDA) and the National Toxicology Program (NTP), have already released comprehensive reports that detail the respective agencies' stances on BPA. As of 2008, the FDA had found that there was no cause for alarm concerning exposure to BPA, while the NTP had found that there is "some concern" with respect for vulnerable groups, namely infants (NTP-CERHR, 2008). Recently, though, FDA has revised its statement on BPA, reporting that it may present a threat to human health, and recommending continued research. The key difference between these two government entities is their authority to actually regulate the substance. Unlike the FDA, the NTP can only give recommendations to other government agencies that can issue regulations. It is important to discern which studies the two groups used to come to their conclusions, and what influences may have affected how government bodies make decisions. Also several state initiatives on BPA regulation are examined for their conclusions.

After an inquiry into the role of government I discuss the current debate over BPA in Chapter 5. This includes the plastic industry's economic concerns associated with BPA regulation, the role of concerned scientists and environmental groups and their appeals to society, and the role of media in portraying the issue.

In Chapter 6 the BPA regulators of other countries are evaluated. Canada has recently banned BPA from baby bottles after it applied the precautionary principle. The European Food Commission, on the other hand, is more in line with the FDA's assessment. They have concluded that there is no risk from exposure to current estimated levels of BPA. The critical research for each country's decision will be identified and

reviewed, along with a discussion of the government's general policies regarding chemical regulation.

Finally, all of these disparate threads will be joined together in Chapter 7 in a discussion to determine if the United States has reached a response threshold for BPA. By looking at the assemblage of political forces, societal influences, and the body of scientific research, I shall draw conclusions about the fate of bisphenol A in the United States.

Chapter 2: The History of BPA

Bisphenol A (BPA) was first synthesized in 1891 by chemist Aleksandr Dianin (Patisaul, 2010). The monomer is formed by condensing acetone with two equivalent parts of phenol. The reaction is catalyzed by the introduction of an acid, typically hydrochloric acid. In practice, a large excess of phenol is used in order to ensure full condensation. The only by-product of this reaction is water.

$$(CH_3)_2CO + 2\ C_6H_5OH \rightarrow (CH_3)_2C(C_6H_4OH)_2 + H_2O$$

Figure 1 – Chemical formulation of bisphenol A (Fiege *et al*, 2002)

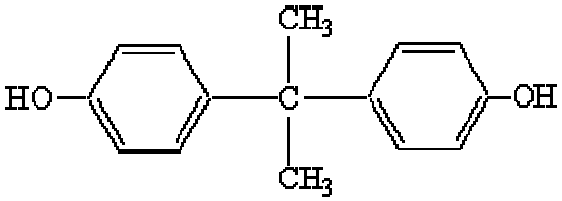

Figure 2 – Chemical structure of bisphenol A (Greener Industry, 2010).

BPA was first suspected of estrogenic activity in the late 1930s. Researchers injected rats, whose ovaries had been previously removed, with a mixture of the chemical of interest and sesame oil in order to ensure uptake of the chemical. Due to the lack of ovaries, the rats could not naturally produce estrogen. Vaginal smears from the treated rats were examined for changes in the cellular makeup due to the presence of an estrogen-like substance. BPA was one of the chemicals that had an estrogenic effect on the ovariectomized rats (Dodds and Lawson, 1938).

Despite what these results might indicate, BPA was introduced into manufacturing in the 1940s and 50s. Since then, BPA has been used in numerous applications, as it is a primary component in polycarbonate plastic and epoxy resins. These plastics are used in countless consumer products, from sporting equipment and medical devices to food and beverage container linings. Production of BPA has increased over the course of time, with approximately 2.3 million metric tons of the substance produced in 2004 (NTP-CERHR, 2007). Currently, Bayer Material Science, Dow Chemical, Hexion Specialty Chemicals, and Sunoco Chemicals are the major producers of the chemical worldwide.

BPA was first assessed for toxicity in 1967 in an experiment that dosed mice and rats with high levels of the chemical in order to provoke a negative response in the experimental subject. The results showed that oral exposure to a liquid solution of the chemical resulted in an LD_{50}[1] at 4.26 g/kg for rats and 2.5 g/kg for mice (NTP, 1982). At the time, this was considered an appropriate evaluation of its acute toxicity in relation to human beings.

BPA did not receive any further consideration until the early 1980s, when the National Toxicology Program (NTP) evaluated the substance for carcinogenic activity. Due to its widespread use in the marketplace, the NTP judged that BPA required additional evaluation beyond the acute toxicity testing of the late 1960s. The research consisted of exposing both mice and rats to BPA mixed into their feed. Based upon the results of the experiment, the researchers concluded the following:

[1] A common term in acute toxicological assessments that refers to a dose that kills 50% of the test subjects.

> The marginally significant increase in leukemias in male rats, along with an increase (not statistically significant) in leukemias in female rats and a marginally significant increase in the combined incidence of lymphomas and leukemias in male mice, suggests that exposure to bisphenol A may be associated with increased cancers of the hematopoietic system. A statistically significant increase in interstitial-cell tumors of the testes in male rats was also suggestive of carcinogenesis, but was not considered to be convincing evidence of a compound-related effect because this lesion normally occurs at a high incidence in aging F344 rats.
> Under the conditions of this bioassay, there was no convincing evidence that bisphenol A was carcinogenic for F344 rats or B6C3F1 mice of either sex (NTP, 1982).

At the same time, researchers were examining the potential teratogenicity of a number of chemical compounds, including BPA. The study injected the monomer into pregnant Sprague Dawley (SD) rats during key gestational days at doses of 85 and 125 mg/kg. These doses caused a number of defects in the developing fetuses, including incomplete ossification of the skeleton and the development of an imperforate anus in a significant number of the fetuses that made it to birth (Hardin *et al*, 1981).

In light of these results, a team of researchers set out to validate and expand the body of knowledge regarding the effects of BPA exposure on a developing fetus. This study, similar to the study reported by the NTP in 1982, delivered BPA dissolved in corn oil to rats and mice. This study dosed pregnant females with the chemical and observed the fetuses for any sign of malformation, such as missing skeletal features or deformed organs. The CD rats received doses of 0, 160, 320, and 640 mg/kg, while the CD-1 mice were dosed with concentrations of 0, 500, 750, 1000, and 1250 mg/kg, values above those considered in Hardin's tetragenicity study (Morrisey *et al*, 1987). While the researchers did note some abnormalities, such as increased maternal liver weight in mice,

there were no reported abnormalities in the resulting offspring. With the publication of this study, BPA seemed to be absolved of any detrimental effects on human beings at low doses. However, a series of discoveries and fact finding would soon find BPA suspect of causing changes at levels below those considered before.

The first event occurred in the laboratory of Ana Soto and Carlos Sonnenschein in 1987. They had been performing an experiment in hopes of finding an inhibitor protein to combat breast cancer. Their experiment consisted of two sample groups of breast cancer cells, one exposed to the potential inhibitor and the other serving as the control group. However, both groups showed definitive growth of breast cancer cells. Soto and Sonnenschein carefully reviewed the experiment, looking for any potential contaminants that could cause this anomalous growth. Finding nothing, they repeated the experiment and obtained the same results. Eventually they came to question the plastic vessels that housed the experimental cells. It was then that they learned that the producer of the plasticware had recently changed the chemical formulation of its plastic. An additive to the plastic that hadn't been there before caused the growth of cancer cells (Soto *et al*, 1991). In the end, the contaminant in question was nonylphenol, not BPA, but it was the precursor to a whole new line of questioning (Colborn, Dumanoski, and Myers, 1997). It provided evidence that there might be harmful chemicals found in the plastics that we humans use daily. And furthermore, it showed that the chemical did not have to be present in high concentrations in order to have an effect.

It was not until the publishing of a study in 1993 by Krishnan *et al*, that BPA itself was found to be leeching out of plastic products. Researchers at UCLA were attempting to discover if a common strain of yeast naturally produced estrogens. To

investigate this they grew the yeast in a culture media that contained distilled water which had been previously autoclaved in polycarbonate flasks. The yeast media was then exposed to estrogens receptors from the uteri of rats. Though the culture media did provoke a response from the uterine cells, the researchers found that the compound binding to the estrogens receptors did not originate from the yeast cells. Taking the yeast culture media, they attempted to identify the substance that was confounding their results. Mass spectrometry and nuclear magnetic resonance spectroscopy indicated that the mystery substance was BPA. When the distilled water was autoclaved in the flasks, BPA leeched from the polycarbonate into the experimental media. Though the estimated concentrations of BPA in the yeast medium were rather low at 10-15 nanomoles[2] (nm), further experiments found a cellular response in cultured breast cancer cells at similar levels (Krishnan *et al*, 1993). The researchers noted that polycarbonate had been found not hazardous by the EPA, the NTP, and many producers of the plastic. However, this new evidence began to raise concern, particularly because most safety precautions had a detection limit of 10 ppb for BPA and the experiment showed responses at much lower levels of the substance. Even so, this was only one study. One study alone cannot influence policy, or convince scientists that the effect was a direct result of this exposure. It would take the concerted effort of many minds to unveil the mystery behind BPA and other chemicals.

The second occurrence that spurred awareness of BPA and other chemicals in commerce was the ongoing research of Theo Colborn. Through the late 1980s and 1990s she was researching a rash of deformities occurring in many animal species in the Great Lakes. Colborn was concerned that toxic chemicals making their way into the Great

[2] Approximately 2 parts per billion (ppb)

Lakes caused these animal maladies. At the time, society predominantly associated toxic chemicals with the development of cancers. Colborn first followed this line of thinking, but found little evidence of cancers in the afflicted wildlife. She reached further, and found research indicating that some chemicals have a feminizing effect on animals. In other words, some chemicals interrupt the natural hormones found in living organisms and cause them to develop in an abnormal manner. Hormones dictate the growth and development of an organism, as well as the day-to-day regulation of bodily functions. Colborn immediately began to reach out to other researchers and to spread her findings throughout the scientific community. In time, Colborn would come into contact with and organize a host of scientists, each with a piece of this overarching puzzle. One of those scientists was Frederick vom Saal.

Vom Saal is a reproductive physiologist working at the University of Missouri. In the early 1980s he published research that showed evidence of very small amounts of hormones having significant effects on the development of mouse fetuses. In his experiment, vom Saal performed caesarian sections on pregnant female mice to observe the positioning and development of the mouse's offspring. Knowing that mouse fetuses are packed tightly together in the womb and that male and female mice require different hormones to develop, vom Saal hypothesized that the doses of hormones a fetus receives might wash over onto adjacent fetuses. Furthermore, if a fetus of one sex was between two of the opposite sex, such as a female between two males, the female would receive a significant dose of testosterone, and vice versa, as depicted in Figure 3. After removing the infantile mice, he observed their behavior as they matured. As predicted, female mice positioned in the womb between two male mice began to show male behavior traits,

while males positioned between two females displayed female behaviors. This experiment demonstrated the vital role hormones play in fetal development, and also that very slight shifts in hormonal levels can result in neurological changes. Changes occurred in females at levels as low as 35 parts per trillion (ppt) of estradiol and 1 ppb of testosterone (Our Stolen Future website, 2010).

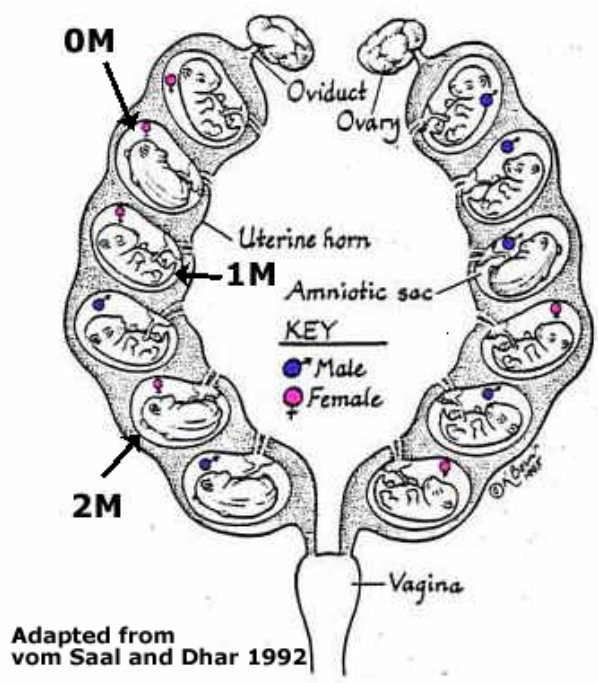

Figure 3 – Diagram depicting fetal positioning in mice (Our Stolen Future website, 2010)

Colborn took this information and worked it into her own research on the Great Lakes. More importantly, though, she introduced vom Saal and his research to other scientists, who began to exchange and generate new ideas. In 1991 she organized the first Wingspread Work Session, in which many scientists of various fields met and exchanged ideas, including toxicologists, zoologists, and endocrinologists. Colborn, along with the help of John Peterson Myers and Diane Dumanoski, would later go on to

publish *Our Stolen Future*, which catalogues the thoughts and ideas originally generated by Colborn and the Wingspread sessions.

Under normal circumstances, the researchers that Colborn brought to Wingspread would have never interacted. It was in this environment that the connection between common, widely used chemicals and the interruption of normal levels of hormones was made, and that the Endocrine Disruptor Hypothesis was formed. It was under conditions such as these that researchers like Sonnenschein, Soto, and vom Saal would meet. It was this synergy of research and intellectual exchange that would fuel the intense research into BPA beginning in the mid 1990s to the present day.

Chapter 3 – The Current Science

With the alarms set ringing by the findings in the laboratories of Krishnan *et al* on the west coast and Sonneschein and Soto on the east coast, along with the publication of Colborn's book, a host of new research was undertaken in hopes to understand the effects of environmental estrogens. Of all the xenoestrogens that have been discovered, none has become more concerning than bisphenol A because of its presence in seemingly endless consumer products.

There are two factors to consider when evaluating the potential risk of human exposure to BPA. The first is to assess the threshold at which harmful outcomes start to occur. There are two overarching methodologies used to assess levels at which BPA can be active in organisms. The first is to perform an *in vivo* experiment, or an experiment which takes place in a living organism. These experiments test the response of the entire system of a living organism to a chemical. The other method is to perform an *in vitro experiment*, which means it takes places in an environment outside of an organism, such as a cell culture in a petri dish. These types of experiments will typically examine specific cellular level responses to a chemical. This literature review will focus primarily on the review of *in vivo* studies, as it is the most relevant to the effects of BPA on complex biological systems that involve multiple organs and metabolic pathways. *In vitro* effects are important for establishing precise cellular and tissue reaction pathways and responses to BPA, but *in vivo* studies examine toxicity as it affects a system rather than a single cell or tissue culture.

The second factor involved in BPA risk assessment of food contact applications is to determine how much BPA is being ingested by human beings, namely how much BPA

a human could be exposed to throughout the day. These studies may examine how much BPA may leach out of the linings of plastic cans, or the migration of BPA from dental sealants. These data can then be used to estimate the amount of BPA a human might ingest throughout a typical day. Another method of determining BPA exposure is to directly sample human blood serum or analyze concentrations of BPA in urine.

This chapter will explore the aforementioned scientific studies that have been conducted since the publication of *Our Stolen Future* in 1996 until the present day. This date was chosen because it marked the widespread acknowledgement and concern that there may be an unseen threat embodied in many of the chemicals we have long assumed to be safe. The most influential studies will be discussed, with particular emphasis on their implications for human health policy. The chapter will conclude with a discussion of the most recent scientific research and how it might influence future BPA initiatives.

Exposure Threshold Determination

Certain types of experiments are conducted by dosing an animal with varying amounts of the chemical in question until a response is seen. With regards to BPA, the major concern is what occurs in reaction to low doses, which are generally accepted to be those below the current "safe" level of 50 mg/kg/day for rodents (Tyl *et al*, 2002). This dosage, at which no effect is seen, is labeled the No Observed Adverse Effect Level (NOAEL). The dose above the NOAEL is then considered to be the Lowest Observed Adverse Effect Level (LOAEL). Policy makers utilize the NOAEL to decide the level to which humans may be exposed without adverse effects, also known as the Acceptable Daily Intake (ADI).

The current practice of determining an ADI from a NOAEL is to apply a series of safety factors that typically reduce the NOAEL in rodents by 1,000 fold. A factor of 10 is applied for the genetic difference between the test animals and humans, followed by another factor of 10 for vulnerable populations such as the elderly and infants, and a final factor of 10 for genetic variability between humans that may result in some humans being more susceptible to a toxin than others. This practice of applying safety factors has long been a topic of debate, as these factors have not been scientifically proven to provide an adequate buffer for human beings. There is uncertainty as to whether or not there is an acceptable margin of safety between effects seen in rodents and potential effects in humans. However, as it is the current accepted method, I shall proceed, for this thesis with the current standard of ADI derivation.

Low dose BPA research began with the publication of two articles published in 1997 and 1998 stemming from the same rodent trial performed in the laboratories of Frederick vom Saal, one of the leading researchers into the deleterious effects of BPA. In 1997, Nagel *et al* published a study that focused on the effects of low doses of BPA on CD-1 mice. Bisphenol A was fed to pregnant mice in concentrations of 2 ug/kg/day and 20 ug/kg/day, and the subsequent offspring were then studied for abnormalities. Male offspring exposed to the lower dose of BPA showed a 30% increase in prostate weight, while those exposed to the higher displayed a 35% increase (Nagel *et al*, 1997). The follow-up publication in 1998 authored by vom Saal *et al* reported adverse effects in additional endpoints in male offspring. At 2 ug/kg/day BPA permanently increased the size of the preputial glands, but reduced the size of the epididymides. At 20 ug/kg/day, BPA significantly decreased efficiency of sperm production (daily sperm production per

gram of testis) by 20% as compared to the control group (vom Saal *et al*, 1998). These two studies were the first reports in the scientific literature questioning the safety of BPA, as both studies stated that negative reproductive and developmental effects were seen at environmentally relevant doses[3].

Two studies cropped up almost immediately to contest the results published by Nagel and vom Saal. Cagen *et al* (1999) dosed pregnant CF-1 mice with 0, 0.2, 2, 20, and 200 ug/kg/day of BPA via oral deposition. Of this range of doses, none produced any effects in the male offspring. One group of mice was used as a positive control and dosed with 0.2 ug/kg/day of diethylstilbesterol (DES). The purpose of this control group is to confirm that the mice are showing the proper responses when exposed to a known, potent estrogen. The positive control group, like the experimental groups, did not show any effects (Cagen *et al*, 1999).

A similar study was published in an attempt to repeat the experiments performed by Nagel and vom Saal. In this experiment, the researchers dosed CF-1 mice with 0.2-2 *u*g/kg/day of DES and 2-20 *u*g/kg/day of BPA (Ashby, Tinsewell, and Haseman, 1999). The authors noted no changes in prostate weight or sperm efficiency in either the experimental or control groups, which were dosed with DES as in Cagen's study. The major contention with these studies revolves around the lack of response from the positive control groups (vom Saal and Welshons, 2006). The rodents were dosed with DES in order to confirm an adverse reaction to a xenoestrogen. Neither of the studies reported any differences between the DES and control groups. It is worth noting that the

[3] Meaning that these are levels of BPA that an average person who is not engaged in an occupation where they are regularly in contact with BPA might be exposed to throughout the day.

Cagen and Ashby studies were performed and funded by the plastics and pharmaceutical industries, respectively.

In 2000 another study was conducted in order to replicate the results seen by vom Saal's laboratory. DES and BPA were orally administered to 15 pregnant CD-1 mice at concentrations of 100 ng/kg/day and 50 *u*g/kg/day, respectively. An additional group was fed 200 *u*g/kg/day of DES as a high dose to compare to previous studies. Similar to vom Saal's original study, the male offspring showed increased prostate weight and decreased epididymis weight (Gupta, 2000).

This study was soon countered in 2001 by Ema *et al*. They conducted an exposure study over the course of two rat generations. The experiment began with an initial adult population of rats (F0) that were given BPA daily at the onset of the pre-mating period and continued through the mating, gestation, and lactation for two generations. BPA concentrations ranged from 0.2-200 *u*g/kg/day. All of the generations (F0, F1, and F2) were then observed and dissected to identify any abnormal development or behavior. The researchers did not identify any aberrations in body weight, reproductive behavior, or neurological behavior. However, the researchers did discover significant differences in anogenital[4] distance (AGD) in some of the experimental groups, including low doses of 0.2, 2, and 20 *u*g/kg/day. Despite these observations, the authors dismissed their results, claiming that while their results were statistically significant in actuality the differences observed were not more than 5% of the average AGD for the rats.

[4] Anogenital distance is defined as the distance between the external reproductive organs and the anal opening.

In 2002 the most influential study for regulatory risk assessment was published by Tyl *et al*. Utilizing Sprague Dawley (SD) rats instead of mice, this study examined the effects of BPA administered over the course of three generations rather than examining one or two generations of offspring. The study considers a variety of toxicity endpoints, including male prostate weight (as examined by vom Saal) but also including a host of other parameters such as individual organ weight and frequency of sexual intercourse. Over the dose range of 0.001-5 mg/kg/day there were no observed effects (Tyl *et al*, 2002). However, some endpoints, such as sensitive neurological development are not examined by the authors of this study. The study has also fallen under criticism for using SD rats, which had been previously proven to be less sensitive to estrogens than the mice used in Nagel and vom Saal's experiment (vom Saal and Hughes, 2005). As if in response to this criticism, Tyl published a similar study in 2008 that used mice instead of rats. The mice were observed for two generations rather than one and dosed with comparable levels of BPA, ranging from 0.003 to 600 mg/kg/day. This study established the same 5 mg/kg/day NOAEL as Tyl's 2002 study. Similar to the Cagen and Ashby studies, which also reported no negative effects, Tyl's studies were financed by many BPA producers as well as the American Chemistry Council.

Though Tyl's 2002 study is still lauded by regulatory bodies as the gold standard for BPA toxicity, research with results showing negative outcomes in response to low doses of BPA continued to be published. Contrary to Tyl's results, Timms *et al* (2005) found developmental effects on the prostate and urethra of CD-1 mice at concentrations as low as 10 *u*g/kg/day, quite different from Tyl's observed NOAEL of 5 mg/kg/day (2005). Research on the neurological effects of BPA was also pursued. Palanza *et al*

(2002) found that female rats exposed to BPA during gestation and in adulthood showed less inclination to engage in maternal behavior.[5]

Some of the more provoking evidence comes from the studies performed by Nishizawa *et al* (2005). Similar to the Palanza *et al* studies used to indentify the lower bound of neurological effects in the NTP-CERHR report, various levels of doses were given to pregnant mice at specific time periods during gestation. The embryos were then monitored during development for changes in mRNA expression in the developing brain and gonads. The results showed a U-shaped dose-response curve, with a marked increase in mRNA expression at 0.02 ug/kg/day, 200 ug/kg/day, and 2,000 ug/kg/day, but no significant increases at 2 ug/kg/day as compared to the control group. However, the one major issue that remains unanswered in this study is whether there is any noticeable difference in the mice after they have been born.

Additionally, a study conducted by Ryan and Vanderbergh (2006) provides evidence of behavioral changes in the offspring due to BPA exposure in the womb. Mice were used in this study as well, but the BPA was administered to them during both prenatal and early postnatal development. The BPA-exposed mice showed increased anxiety when placed in a maze or given the choice between a light or dark compartment. The study provides a NOAEL of 2 ug/kg/day and a LOAEL of 200 ug/kg/day (Ryan and Vanderbergh, 2006). In light of the results seen by Nishizawa *et al* (2005), it would be interesting to see if there are any different behaviors at 0.02 ug/kg/day.

To summarize, the science on the matter of the toxicity of BPA is conflicting. Some studies report no detrimental effects at low doses, while others find evidence of estrogenic activity at surprisingly low levels. It should be noted that as of 2005, of a total

[5] Defined as time spent feeding young and time spent in the nest.

of 105 studies, 94 found harmful outcomes following exposure to low doses of BPA (vom Saal and Hughes, 2005). While the supposition could be made that the quality of those 11 studies showing no effect is greater than the 94 showing negative effects, the disparity in quantities is somewhat significant. Therefore, it can be concluded that the majority of studies have observed an adverse effect following exposure to low doses of BPA.

Sources and Exposure Estimates

While it is certainly important to establish the thresholds at which negative effects begin to occur, this information is not useful unless it is possible to determine the levels of BPA that actually occur in the bodies of humans. Based upon vom Saal's research, we might establish an ADI below 2 ng/kg/day.[6] In the eyes of a regulator, if this level is never reached over the course of a day there is no need for concern.

One of the first questions that must be asked when considering the amount of BPA that is ingested per day is where and in what food contact applications is BPA being found? Furthermore, once an item is suspected of containing BPA, the amount of monomer that is finding its way into food and beverages must be estimated.

Canned foods and beverages make up a large proportion of the food-related products that contain BPA, which can leech into consumable items. Aluminum and tin cans are typically lined with an epoxy to prevent the contents from interacting with the metal. Heat and acidity cause BPA in the epoxy to migrate into the contents of the can at a higher rate. Research into the potential concentrations of BPA found in canned products

[6] Since vom Saal observed an effect at 2 *u*g/kg/day in mice, we would take that number and divide it by a factor of 1,000.

began as early as 1995. One study reported a maximum migration of 33 *u*g/can of food (Brotons *et al*, 1995). At first glance this may seem insignificant, since an adult that weighs 70 kg would be exposed to approximately 0.47 *u*g/kg by bodyweight. However, when considered in terms of an infant that may weigh 4 kg, this exposure would be 8.25 *u*g/kg, significantly above our assumed ADI of 2 ng/kg/day. This is after consumption of only one can of food, under the conditions of this study. Other studies have found concentrations ranging from 0-842 *u*g/kg. While these numbers span a broad range of values, including the absence of BPA in some cases, it is disquieting to know that there can be higher than expected levels in the cans of vegetables one keeps in the cupboards.

However, canned vegetables may not be the only vegetables at risk of containing BPA. In 2003 a study was released that reported a range of 0.25 to 1.1 mg/kg in fresh vegetables (Vivacqua *et al*, 2003). Though this study has not been replicated, neither has it been disproved by a subsequent study. Presumably this is a food item that is not stored in an enclosed plastic or epoxy-lined container, suspended in water[7], and yet BPA was found in surprisingly high concentrations when compared to canned foods. There was no discussion about how BPA might have made its way into the fresh produce. If BPA is found in fresh foods, where else might it be found?

While foods and beverages are thought of to be the major source of exposure, BPA has been found in unlikely places. In 1996 a study was conducted to explore the amount of BPA that might leach out of dental sealant, another product known to contain the monomer. The study reported a maximum of 0.62 ug/ml in 27 ml of saliva leaching from the dental sealant 2 hours after application (Olea *et al*, 1996). This study came under criticism later as only one patient exhibited such a high concentration of BPA.

[7] Which would provide a media for BPA to travel from the plastic to the vegetable.

Critics of the study claim that "due to what is known about the migration of phenols such as BPA in dental applications, the sealant applied at the time would have had to be in excess of a gram, likely many grams. And if so, this type of unusual treatment should have been carefully documented (Ashby, 1997)." Similar levels of BPA leeching from dental sealant have not been reproduced to date. Yet in light of this the fact remains that dental sealant contains the monomer, and that it is capable of migrating. Another study found BPA present in recycled paper at concentrations of 0.19 to 26 *u*g/g (Ozaki *et al*, 2004).

These examples serve to highlight the variety of avenues that BPA might take to be introduced into the human body through ingestion. Regulatory agencies use these studies to estimate the amount of BPA that the average person ingests in a day. Some believe that these estimates are failing to account for levels seen in examinations of human body fluids.

Observed Levels of BPA in Humans

Estimates of the amount of BPA that individuals may be consuming are a useful tool for establishing regulations to limit exposure to the chemical. However, they do not offer concrete evidence for establishing how much BPA can be found circulating through a human body at any one time. Therefore, researchers have also studied how BPA is transported through the human body as well as how much BPA exists in the human body at any given time.

Before considering how much BPA might be in a human body over the course of a day, it is important to determine how long it takes for one's body to process and excrete

the chemical. Unlike contaminants such as DDT and PCBs, BPA is not a compound that filters into fatty tissues where it resides for many years. Studies have shown that BPA has a half-life of less than 6 hours in the human body (Völkel *et al*, 2002). Rather, the concern revolves around the presumably chronic exposure to foods and other materials that have traces of the chemical, which can keep concentrations in the body at a static level throughout the day.

There have been many studies measuring the amounts of BPA in human urine. One of the earlier urine studies performed by Ouchi and Watanabe (2002) found levels ranging from 0.6 to 71.4 *u*g/day. Another study found mean concentrations of 1.33 *u*g/L, with a median value of 1.28 *u*g/L per urine sample (Calafat *et al*, 2005). Research examining BPA levels in children found a mean of 3.4 *u*g/L, with a maximum of 40 *u*g/L (Wolff *et al*, 2007).

When considering these values there are many variables to take into account. Can the experimental subjects involved be considered "average" human beings, with "average" diets? How many times a day do the individuals urinate, and in what volumes? Do any of the subjects drink a great deal of water, which may dilute the presence of BPA? Or does this exacerbate the problem as they might be drinking water from containers made from or lined with BPA? These are but a few of the variables that may be important in measuring excreted BPA. While the amount of BPA present in these types of studies fluctuates, the fact remains that humans ingest measurable amounts of the chemical each day.

Other researchers have attempted to measure the levels of BPA present in human body fluids, particularly in pregnant women, as there have been a number of studies that

have reported adverse effects resulting from prenatal exposure to the chemical. As noted above, there is evidence of BPA causing developmental effects in organisms. Therefore, there is concern that pregnant women being exposed to levels of BPA may inadvertently be exposing their unborn children to the chemical. One of the most influential studies was published by Schonfelder *et al* (2002). The study focused on measuring the amount of BPA present in pregnant women, their fetuses, and placental tissue. The research found concentrations ranging from 0.3 to 18.9 ng/ml in the mother's plasma, 0.2 to 9.2 ng/ml in the fetus' plasma, and 1.0 to 104.9 ng/g in placental tissue (Schonfelder *et al*, 2002). Another study found that levels of BPA were higher in the amniotic fluid at 15 weeks gestation (Ikezuchi *et al*, 2002). These and other studies confirm that fetuses are being exposed to BPA during critical stages of development in the womb.

Conclusions from Toxicological Studies

Today, the scientific debate over the dangers of BPA continues. Recently a study was published in *JAMA* using a relatively new data set that measured a number of human health concerns in relation to urinary BPA levels. The study found positive correlations between elevated BPA levels and a variety of common human health issues, including diabetes, obesity, and heart conditions. The researchers acknowledge that these results must be repeated to certify their findings, and that some degree of causality must be established (Lang *et al*, 2008). The major question is whether or not the elevated BPA levels caused the health issues, or if the health issues change human physiology in such a way that the body no longer flushes BPA through the system as quickly. In fact, the elevated urinary BPA concentrations in obese individuals may simply occur because they

consume more food, and so have a higher BPA intake. Finally, this study is only cross-sectional, meaning that it only gives an idea of what is happening at one point in time. For a study of this type to have more merit, it must provide longitudinal data. However, a number of complications may rise, simply due to the fact that one cannot establish a control group, as most people are exposed to BPA on a daily basis. Furthermore, one cannot ethically dose an experimental human subject with a suspected harmful substance.

Consider the implications if this study accurately predicted the effect of BPA on the population. Suppose by eliminating BPA a number of common maladies, including heart disease and obesity, could be avoided and create a healthier standard of living for everyone. At the same time, to abruptly ban the use of the chemical could impact a significant part of the packaging segment of food production, and to do so without reasonable evidence would cause unnecessary problems. It is up to US regulatory bodies to assess the validity of this and other studies on BPA, and to decide whether there is a threat that requires regulation to be put in place.

Chapter 4 –Regulatory Authorities and Their Stances

When considering broad public health issues, the United States has several avenues through which to assess the concerns as well as establish policies to prevent undue harm to public health. On the one hand, having a number of federal regulatory authorities consider the same issue can provide more insight, as the efforts of more people with varying specialties bend their minds to the task of risk assessment and policy solutions. However, it can also give rise to a situation where overlapping assessments may cause further confusion if the results oppose one another. Furthermore, if any action is to be taken, conflicts may arise as jurisdictions over public health issues cross paths.

In the case of BPA there are three government institutions that have a stake in the assessment and, in some cases, regulation of the chemical. They are the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the National Toxicology Program (NTP), which consists of a consortium of agencies. Of these entities, only the NTP is unable to draft regulations. The NTP can only provide assessments and give recommendations to those entities that can institute regulations or pass new legislation.

Additionally, should these agencies prove insufficient to the task of establishing new regulations, legislative bodies can step in and establish policy in the same way that new laws are issued in our government. These initiatives can occur at any level of government, including local, state, and federal levels, though as the scale of jurisdiction is increased there will be a greater amount of public opinion needed to sway representatives, as congressmen and senators represent a great many more individuals than a city or county official.

The Food and Drug Administration

The United States Food and Drug Administration is the government entity responsible for assessing the quality of food and drug products and for the establishment and enforcement of policies ensuring that these products are safe for public use. The origins of the FDA extend back to 1906 with the passage of the Pure Food and Drugs Act, which prohibited interstate commerce of adulterated and misbranded food and drugs. It was not until 1930 that the FDA was officially organized and given the name it bears today.

Since the greatest exposure route of BPA is through the consumption of everyday food and beverage products, the FDA finds itself at a pivotal point regarding the evaluation of BPA as a threat. Even if the FDA did not create any laws itself, it would be responsible for enforcing and upholding any legislation that might be passed by higher authorities. Therefore, the FDA finds itself under much pressure from stakeholders to make an appropriate decision.

The FDA released its draft assessment of BPA exposure due to food contact uses in August of 2008, a few months after the NTP Center for Evaluation of Risks to Human Reproduction (NTP-CERHR) released a draft of its assessment. The FDA's report has yet to be finalized, mostly due to the findings of a subcommittee formed to peer-review the report. Though the FDA acknowledged that while the two regulatory bodies are set to achieve the same goal of a determination, they stated that they are both independent agencies and as such will have independent reports. However, because the NTP draft report was released before the FDA's draft assessment, the FDA was able to partially

base its judgment on the NTP's findings. For example, the FDA concluded that it would only consider issues that the NTP labeled were of "some concern," which means that they did not consider the effects of BPA exposure on pregnant women or reproductive effects on non-occupationally exposed adults (FDA, 2008). Based upon their review of the science, the FDA set their No Observable Adverse Effect Level (NOAEL) at 5 mg/kg/day.

The FDA draft report relies heavily on two mice studies performed by Tyl et al in 2002 and 2008 for this NOAEL. These studies were used exclusively to make its determination on reproductive toxicity, and seen referenced again throughout the assessment. As discussed in the previous chapter, studies are notable in that they were performed with multiple generations of mice, allowing for a more longitudinal view of the effects of BPA. The mice were monitored for many parameters, which the FDA used as grounds to base their assessment primarily on these two studies. The studies were specifically designed to include a large sample population to provide a greater strength of evidence. The NOAEL of 5 milligrams/kilogram per day (mg/kg/day) suggested at the conclusion of the FDA's draft assessment was drawn from Tyl's 2002 study. According to the FDA, this provides a margin of safety[8] of 2,000 for infants and 27,000 for adults, based upon their exposure estimates (FDA 2008). However, the Tyl study strictly examines parameters such as body weight and organ weight, which do not characterize neurological disorders. Additionally, the results may be in question due to the fact that Tyl's studies were funded in part by the plastic industry (NTP-CERHR, 2008).

[8] In this case, the margin of safety is the magnitude of difference between the FDA's predicted daily dose and the NOAEL of 5 mg/kg/day.

Following this draft assessment, an FDA Science Board Subcommittee was convened to review the report. The Subcommittee issued its peer review statement in late October 2008. In addition to other researchers, the subcommittee received a presentation by Frederick vom Saal, a leading researcher of the effects of BPA on human health. The subcommittee criticized the original report for relying so heavily on the Tyl studies. It charges that the FDA failed to consider studies which other expert panels, namely the NTP-CERHR group, identified as having utility and that suggested that the NOAEL might be lower than 5 mg/kg/day. The Subcommittee also found that the FDA needed to examine more studies regarding infant exposure, as its draft report only identified 14 types of infant formula in its risk assessment. Furthermore, the Subcommittee judged that the draft report did not adequately assess the cumulative effect of doses from different sources when estimating daily exposure to BPA. The Subcommittee found these and a few other deficiencies to be substantial enough to state that the FDA's claim that the current margins of safety are adequate is false, and that it should be reconsidered using a wider body of literature (FDASBS, 2008).

Due to the review of the Subcommittee the FDA was forced to delve more deeply into the literature surrounding the health effects of BPA. In comparison to assessments performed by the National Toxicology Program and other nations, the FDA draft assessment is very brief, and leaves out much detail that is covered in other assessments.

The FDA has since changed its stance on BPA after further review. In January of 2010 the FDA issued a statement saying that it has "some concern" regarding the effects of BPA on child development (FDA, 2010). However, the release did not make any

statements regarding official regulation of the substance. Rather, they placed the onus on consumers to avoid BPA containing products if they so wished.

The National Toxicology Program

Released in early September 2008, the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A is the culmination of a series of expert panel discussions and literature reviews held over the time period of 2006-2008. This assessment of BPA, unlike the FDA's draft report, stated that there was cause for concern due to human exposure to BPA. The NTP stated that there is:

- "Some concern[9]" for the neurological development of fetuses and infants exposed to BPA.
- "Minimal concern" for BPA's effect on the mammary gland and early onset of puberty in females. This was originally labeled of "some concern" but was later revised after further consideration.
- "Negligible concern" regarding the exposure of pregnant women to BPA and the potential for fetal mortality, birth defects, and other potential birth issues.
- "Negligible concern" regarding reproductive effects in anyone non-occupationally exposed, and "minimal concern" for those occupationally exposed.

In a base comparison to the FDA draft assessment, the NTP-CERHR has evaluated a much greater body of literature. In presenting their exposure estimates the NTP-CERHR presents both the maximum reported values of BPA found in humans alongside the range of daily dose estimates calculated by various studies. However, unlike the FDA, the NTP-CERHR does not recommend a NOAEL or Lowest Observed Adverse Effect Level (LOAEL). The NTP-CERHR specifically states that there is no

[9] The NTP has 5 levels of concern when assessing potentially toxic substances. "Some concern" falls in the exact middle of the scale, with "minimal" and "negligible" making up the lower two levels of concern and "concern" and "serious concern" comprising the upper levels..

conclusive evidence for human effects with regards to developmental and reproductive toxicity. Instead, the report presents the animal testing data that exists. The majority of the data presented with regards to developmental toxicity do not appear worrisome as there were no effects to the rodents up to concentrations as high as 148 mg/kg/day. The conclusions for reproductive toxicity are slightly more troubling, which states that there are NOAELs of 47.5 mg/kg/day in female rodents (LOAEL: >475 mg/kg/day) and 4.75 mg/kg/day (LOAEL: >47.5 mg/kg/day). However, the data on neurological development is most concerning. The report states that rodent studies "suggest that bisphenol A causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice (0.01–0.2 mg/kg/day)" (NTP-CERHR, 2008).

The lower limit of this range was provided by a study performed in 2002. The study involved feeding pregnant mice either a measured dose of corn oil or 10 micrograms per kilogram (ug/kg) dose of BPA daily during days 14-18 of gestation. The females birthed of these mice were then impregnated and were then given the same treatment, either plain corn oil or BPA orally administered, as their mothers. The resulting experimental groups consisted of mice entirely unexposed, groups prenatally exposed to BPA either during the second or third generations, and a final group that had been dosed for both the second and third generations. The study showed that females in the final generation who were exposed to the BPA either during gestation or during pregnancy had reduced maternal behavior. Maternal behavior in the female mice was defined as nesting or feeding the infantile mice, rather than grooming themselves or being active outside of the nest. Those exposed to both did not show significant differences as compared to the control group. Though the double exposed females did not show

different behavior, the fact that some of the mice responded provides adequate evidence to generate concern for doses as low as 10 ug/kg/day during gestation (or 0.01 mg/kg/day) (Palanza *et al*, 2002).

To summarize, the NTP-CERHR report reads very differently from the FDA draft assessment. For one, it is much more comprehensive, including estimates for environmental exposure. It also provides a detailed review of each study considered in the report. However, it does not appear to attempt to set an exposure threshold for human beings, even by applying margins of safety, however arbitrary the process is. At most, the report concludes that more research is necessary to determine if there is an effect on humans.

The Environmental Protection Agency

Established in 1970 due to the growing concerns over the declining quality of US water and air, the Environmental Protection Agency's (EPA) mission is to protect human health and the environment. The Agency's formation was fueled in part by the publication of Rachel Carson's *Silent Spring*, which documented the effects of pesticides on wildlife and human beings. While the book was released with much skepticism from corporate America and the politicians who supported them, Carson left an indelible mark upon the fabric of American environmentalism.

Upon its formation, the EPA was issued two tasks; to repair the damage already done to the environment as well as the establishment of new rules and protocols to avoid causing more damage in the future. With regards to BPA, the EPA would be mostly concerned with the effects of the chemical on the environment as well as environmental

exposures to human beings, such as through contact by public waters and through exposures in the workplace. Recently the EPA has issued a statement stating that the FDA has the principal responsibility for BPA, as the main pathway of exposure is understood to be through food products. At the same time, legislation is being proposed that might bring BPA back into focus under the Toxic Substances Control Act (TSCA) as new concerns are being raised. This action would increase the influence that the EPA has over the chemical as it is released into the environment, yet at this time the proposition is merely in discussion.

As we have already established, because the primary route of human exposure is through foods and beverages, the EPA would be left out of this discussion. While humans may be exposed to BPA through the environment, it is likely not as substantial a threat as presented by food-contact applications. However, if the EPA were to release guidance on the chemical it would certainly influence any decisions made by the FDA.

Local, State, and Federal Legislative Efforts

As time passes and the public continues to hear indecision from the regulatory authorities over the fate of the chemical, individuals have reached out to their legislative representatives in an attempt to bypass these agencies for a quicker resolution. Since early 2009, a number of bills have appeared at the local, state, and federal level in an attempt to limit or ban the amount of public exposure to BPA. Though these bills initially met with failure, as time has passed and public awareness of BPA has grown, BPA has been given a limited ban in a number of localities.

California was one of the first states to propose a ban on BPA. The state has long been on the forefront of progressive environmental regulation, having secured its own standards for a number of environmental concerns. Introduced in the state Senate in early March of 2009, the bill proposed to ban BPA in baby bottles, toddler sippy cups, and other products that might threaten child development. Initially it seemed that the bill would meet with success, as it was passed by the Senate. However, despite the state's inclination for environmental activism, the bill failed in the California state Assembly by a narrow margin in September 2009.

Concurrently, similar bills were proposed and passed in Suffolk County, NY, the cities of Chicago and New York, and the states of Minnesota, Connecticut, Washington, Wisconsin, and Maryland, while many other states now have bills in active consideration (EWG, 2010). Nearly identical in nature, the legislation forbids the sale of baby products containing BPA. These successes serve to emphasize the public interest and desire in banning BPA in consumer goods. Yet, while safeguarding our children during early development is extremely important, the question remains whether or not more should be done.

As discussed in Chapter 3, BPA has been shown to effect organisms during all stages of development, particularly during gestation. If it is correct to infer that these results can be extrapolated to humans, then it would seem appropriate to develop legislation that prevents pregnant mothers from being exposed to the chemical, which these current bans do not.

At the federal level, the debate continues over taking action against BPA. Senator Feinstein has spearheaded the effort, and presented the "Ban Poisonous Additives Act" in

early 2009. The legislation would ban the sale of reusable beverage containers that have BPA in their formulas, prohibit the release of other food and beverage containers from being introduced into the market, and issue renewable 1-year waivers for manufactures that cannot find a substitute to replace BPA in their products (Feinstein, 2009).

This proposed legislation has been met with praise and support by non-governmental organizations such as the Environmental Working Group (EWG). Yet at the same time industry has scorned and criticized the bill. As with all political issues, a host of interest groups seek to sway public opinion, and use a variety of strategies in attempt to persuade individuals to their agenda. In the next chapter I shall discuss the non-governmental stakeholders and their arguments regarding the threat, or safety, of BPA in food and beverage containers.

Chapter 5 – Non-regulatory Actors and the Ethical Arguments Surrounding BPA

Further complicating the issues surrounding BPA are the continuing debates among impassioned stakeholders. Chemical manufacturers would have the public believe that it is perfectly safe for use in a wide variety of products, including containers and liners for many foods and beverages. Leaping to respond to an unconfirmed threat, they say, would be a waste of time and resources. Concerned scientists and environmental activists, on the other hand, claim that BPA is a dangerous chemical that could be the cause of a host of human maladies, and is particularly dangerous to developing infants. This chapter focuses on the ethical principles behind a restriction on the use of BPA, and the actors that represent each side of the BPA issue.

Policymakers will often look to science to determine the relative safety of chemicals and their effects on human beings. As previously discussed, the science is still conflicting. Though BPA was known to have estrogenic effects as early as 1938, its commercial use began because there were no obvious health effects observed (Dodds and Lawson, 1938). There was an indication that BPA produced estrogen-like effects but the utility of the chemical outweighed this evidence. After all, how threatening could additional estrogen be? It certainly did not kill outright. Our understanding of the complex hormonal pathways was a shadow of what we understand today. Even so, we still remain ignorant to many of the chemical pathways that our bodies depend on. It wasn't until the 1990s and the formulation of the endocrine disruptor hypothesis that BPA became suspect for adverse health effects at low doses. Since then there have been a number of studies produced.

Over a hundred studies have been published that show highly adverse effects due to exposure to BPA. They are primarily experimental studies performed on rodents, as our societal ethics disallow direct treatment of humans with BPA. Several studies have reported irregular reproductive development, resulting in enlarged prostates (vom Saal *et al*, 1998; Gupta, 2000). Other reports show negative impacts to the female reproductive system (Markey *et al*, 2001), and that BPA can stimulate the growth of breast cancer cells (Krishnan, 1993). There are also experiments that show effects on the neurological development of rodents, such as reduction in maternal behaviors (Palanza *et al*, 2002) or increased signs of stress and panic (Ryan and Vandenbergh, 2006). However, there are also studies that refute the results seen in these aforementioned studies, reporting no adverse effects in male development (Cagen *et al*, 1999; Ashby *et al*, 1999) and no abnormal development in males or females over multiple generations with low doses of BPA (Tyl *et al*, 2002).

One might question why there exists such conflict within the scientific arena. There is some conjecture that there might be a conflict of interest related to the progeny of the funding behind these studies. As of 2007, a disproportionate number of studies that were performed with government funding found adverse effects in response to BPA exposure (Rust, Spivak, and Kissenger, 2007). Conversely, all studies funded by the chemicals and plastics industry showed no negative outcomes (vom Saal and Welshons 2006). In a sense it is reminiscent of the conflict over tobacco. In response to studies showing that cigarette smoke caused lung cancer, the tobacco industry responded by producing studies that found no relationship. The resulting confusion caused delays in

protective legislation as policymakers attempted to sort out the "good" science from the "bad."

At its heart, the ethical debate revolves around the idea of the precautionary principle, which states, "if there is uncertainty, yet credible scientific evidence or concern of threats to health, precautionary measures should be taken. In other words, preventive action should be taken on early warnings even though the nature and magnitude of the risk are not fully understood" (Tickner, Raffensperger, and Myers, 1998). The precautionary principle is an option in situations where there is some evidence the public may be at severe risk but no scientific consensus can be reached. The burden of proof is placed upon those who claim that there are no negative outcomes. The product or activity shall not be considered safe until it is determined to be safe. In the case of BPA, the precautionary principle would dictate that BPA should be removed from all products because there are scientific studies that show harm resulting from levels of exposure to which humans can be subjected. Canada, for example, enacted the precautionary principle when it banned baby bottles containing BPA. Rather than expose that portion of the population to a potential risk, the government chose to eliminate it.

In the United States there are no federal restrictions at all for BPA, beyond an Acceptable Daily Intake (ADI) standard of 50 *u*g/kg body weight/day (FDA, August 2008). It is ultimately a few key stakeholders that will decide whether or not BPA sees any restrictions. These stakeholders can be neatly divided into three camps: those who do not want to see restrictions (namely the plastics industry); those who would see tighter regulations; and those who create regulations. Their potential ethical concerns shall each be discussed in turn.

Industry and the American Chemistry Council

Currently in the U.S there are four major manufactures of BPA. They are Bayer Material Science, Dow Chemical, Hexion Specialty Chemicals, and Sunoco Chemicals (Newsday 2009). These are large corporations, which wield vast resources and influence within the political realm through interest lobbies. Above all, the responsibility of a corporation is to its shareholders, which traditionally place profit as the primary objective.

In 2004 approximately 2.3 million metric tons of BPA were manufactured worldwide (NTP-CERHR 2007). At a price of approximately $1,251[10] USD per metric ton this rate of consumption accounts for approximately $2.9 billion[11] of direct sales for the global plastic industry. It is not surprising that this industry would not want to lose this potential income based upon scientific results they feel cannot be successfully replicated. More importantly, removing BPA from commercial could potentially disrupt production lines for untold amounts of consumer items. Without a sufficient weight of scientific evidence showing that BPA will cause harm, corporations will not change their stance on BPA-containing products for it will reduce their ability to make profit. However, beyond revenue there exist other ethical arguments for the continued use of BPA.

The first argument that could be made is that BPA is used in so many products that replacing it would cause a great disruption in the availability of common consumer

[10] This price based upon the median value of 945 Euros per ton as reported in the European Union countries in January 2009 (Mellor, 2009).
[11] Figure obtained by applying an average exchange rate of 1.3244 for the month of January (FRB, 2009), multiplied by the 2004 global production value. This figure is by no means an exact measurement of 2004 BPA revenue. It is merely meant to provide insight to how much BPA itself is worth.

products. BPA is used in the manufacture of compact discs, housing for electronic equipment, and sporting goods, as well as in food contact applications. To find a replacement that is as easy to produce, comparable in production costs, and found to be safer than BPA may take a great investment of time and resources. If reformulated products are in fact higher in price than products containing BPA, low income individuals may not be able to afford BPA-free products. In a sense, "safe" BPA-free products would only be for those who could afford them, unless industries were to take a loss. However, as important as convenience and affordability are, industry can claim that BPA is indispensable for its applications in many medical supplies.

BPA is used in the making of polycarbonate blood oxygenators, dialyzers, and incubators (Polycarbonate/BPA Global Group, 2007). These products are crucial for the care of individuals who are facing serious medical issues. The effects of BPA are normally studied by orally administering the monomer to test animals, as it is the most likely route of exposure for humans. Therefore, the effects seen are usually after BPA undergoes a certain amount of metabolism. In this scenario, BPA is potentially introduced directly into the blood, and from there to other vital organs. A study has shown the prematurely born infants that need the assistance of BPA-containing medical devices have higher concentrations of BPA in their blood than the general population (Calafat *et al*, 2009). If legislation is passed to ensure that no individual is exposed to a certain amount of BPA per day, these medical devices will have to be modified.

In the event that BPA is restricted from use in any product, is it possible to find a replacement compound for use in these medical devices? The ethical dilemma now comes to a choice of ill-defined risks. It may be safer to find another product to use in

these vital medical devices rather than risk exposure to BPA, or perhaps there is no other compound, and BPA must be used in this application. Is it more ethically correct to potentially reduce exposure to BPA, or to delay treatment for life-threatening conditions, assuming there are no good substitutes? In any event, even if BPA were restricted from use in medical devices, there would have to be a period of time in between the adaptation of new products and the discard of the old. Under these urgent circumstances the precautionary principle falls to the wayside.

Substitutes do exist for BPA. Thermo Fischer Scientific Inc., the creators of the ubiquitous Nalgene shatter-proof plastic water containers, changed the formulation on their original polycarbonate bottles and released BPA-free bottles in 2008 in response to consumer concerns. A number of baby bottle manufacturers have also made BPA-free bottles available. Whether this type of plastic is appropriate for use in all applications is unknown to this author. Epoxy resins for aluminum cans can also be modified to reduce BPA migration, as seen in Japan. In response to public concern, a number of manufacturers changed the film lining in food and drink containers. Manufacturers were able to reduce BPA concentrations in can linings without any significant capital investment (AIST, 2007). However, there have been no comprehensive studies that examine the costs and safety of BPA substitutes, and how industries would need to change to adapt to them.

Recently, Sunoco has stated that it will no longer sell BPA for use in products for children less than 3 years of age because the safety of the chemical cannot be proven (Kissenger, 2009). While this is an admirable step, BPA is still being produced by other companies to manufacture countless products for children. Regulations will be needed to

goad industry to abandon BPA. Part of the issue is the US's current climate of chemical regulation. Due to the large amount of chemicals that are used throughout industry, the general practice is to use a product unless it is proven to be a threat to human health. BPA is a chemical that has already been screened by the National Toxicology Program in 1982. As it has already been determined to be "safe" with certain exposure limits, it will be that much harder to convince regulators and industry that BPA is active within the human body, particularly using new low-dose methodologies.

The industry claims that BPA is perfectly safe in consumer products at its current levels. However, industry has a vastly different system of values that guide its actions. Typically industry will follow the path of profit maximization as dictated by its business model. This does not always lead to an outcome that also favors the interests of the public at large. Consequently, in response to an industry that oversteps its bounds, a group of concerned individuals may sometimes arise to inform the public.

The Environmental Working Group and Conscientious Scientists

In many situations that concern human health issues and exposures to potentially dangerous chemicals, environmental groups may take action to inform the public to the dangers of the product in question. The Environmental Working Group (EWG) is the foremost non-governmental organization (NGO) that has lobbied against the continued, unrestricted use of BPA.

Founded in 1993, EWG is a collection of scientists, lawyers, and policy experts devoted to raising public knowledge of potentially threatening chemicals. Specifically, it is EWG's goal "to protect the most vulnerable segments of the human population—

children, babies, and infants in the womb—from health problems attributed to a wide array of toxic contaminants" (EWG, 2010). This mandate alone makes BPA awareness a prime objective of EWG as research has shown that overexposure to estrogenic chemicals can effect neonatal development.

NGOs have proven to be wildly successful in driving environmental policy decisions, particularly in the field of toxic chemicals. A prime example of this can be seen in the case of Alar, a compound that was once applied to regulate the growth of apples. A number of studies were published that reported tumor growth in lab animals exposed to Alar, the trade name for diminozide. The Natural Resources Defense Council (NRDC), another prominent environmental NGO, skillfully used media outlets to inform the public that residues of this chemical were still present on apples and apple products at the supermarket that placed their children at a cancer risk. Consumers, concerned for their wellbeing as well as the health of their children, refused to buy apples products that were suspected of having Alar residues. Farmers in turn stopped using Alar, and as a result the chemical manufacturer completely stopped producing the substance (Krimsky 1995). Without the efforts of the NRDC to inform the public, produce with Alar residue might still be present in supermarkets today.

The efforts of EWG and other NGOs are supported by scientists such as Frederick vom Saal who, after discovering that doses of BPA, lower than the ADI for humans, caused altered development in the reproductive tracts of male mice, began to speak out publicly about the negative effects of BPA exposure. Traditionally, scientists are taught to be objective in their methods and interpreting their results. This objectivity results in a detachment from policy outcomes that are supposed to be decided by scientific facts.

However, vom Saal and his peers likely feel a moral obligation to report to the public their results as well as the results of other studies that highlight the adverse effects of BPA at levels that individuals may be exposed to on a daily basis. As they discovered these phenomena and understand it best, they may consider it a moral imperative to warn the public of the threat of BPA.

Contrary to the beliefs of industry, the EWG and the group of vociferous scientists contend that BPA poses a serious threat to human health. To that end, they would argue that BPA must be removed from any applications where humans may ingest the monomer, particularly in products designed for infants. Ethically, this would mean other factors, such as cost, would not be a deciding issue for them; phasing out BPA is the prime objective.

Their main strategy for initializing tighter BPA regulation is to emphasize the effects of BPA on infants and children. From an ethical standpoint, many individuals place the safeguarding of infants before themselves. Since infants and children are not fully developed they are extremely vulnerable to a host of threats an adult is equipped to handle. At such a young age, even common maladies such as the flu can prove fatal. Unlike the flu, however, toxic chemicals are a product of human ingenuity. They can be controlled, particularly BPA, which is only added because of convenience and tradition in production cycles. Furthermore, BPA acts like a hormone, and may significantly impact the normal growth of a child. One of a parent's worst fears is that their child will not be able to experience a full and happy life. Ethically, if it is possible to eliminate a threat to a child, then any action necessary should be taken. By NGOs and scientists

communicating the message that BPA is harmful to developing children, consumers are responding by demanding BPA-free products from industry.

The recent bans of BPA-containing baby bottles show the power of this ethical imperative. Canada is the first and only country to institute a nation-wide ban. However, restricting the use of BPA in baby bottles does not safeguard children from exposure to BPA wholesale. The epoxy lining in cans containing baby formula also contains the substance. While banning baby bottles may be the first victory in restricting the use of BPA, it is far from absolute protection for developing children.

Ultimately, an argument can be made that exposure should be limited regardless of age. If the material is already considered to be harmful to children, it isn't an unreasonable assumption to conclude that there may be effects in adults. Furthermore, the results of some animal studies have shown effects on the reproductive systems of adult mice (vom Saal *et al*, 1998). There is also the danger of fetal exposure when a pregnant woman ingests BPA (Schonfelder, 2002). While individuals can attempt to steer clear of food and drink products that contain BPA, it would be safer to not use the substance at all.

Regulatory Implications

It is ultimately up to the government to decide whether or not BPA is to be regulated. Industry will try to use its resources and connections to forestall any legislation that is perceived to be an over-reaction, while the environmental NGOs and involved scientists will inform the public of the dangers and lobby for stricter controls.

Federal, state, or local government may introduce measures to regulate to the distribution of BPA-containing products.

At the federal level, any regulation on BPA in food contact applications or medical devices will come from the FDA. While the Environmental Protection Agency (EPA) also has authority to regulate BPA, their sphere of influence does not extend to the major sources of exposure to the general population, namely food. While it is possible to be exposed to BPA in the environment, it is unlikely due to the short half-life of BPA in water. Food contact applications, on the other hand, are encountered on a daily basis.

The FDA released a draft of its assessment of BPA in the spring of 2008. The report concluded that the current level of BPA exposure was not a risk for any human beings, even infants. The assessment quickly came under criticism for its reliance upon a very few industry-funded studies. A peer-review of the assessment was issued in October, highlighting many of the concerns voiced by FDA critics. The criticism was mainly focused on the short-sightedness of the FDA's assessment, particularly in light of the much more comprehensive review of BPA performed by the National Toxicology Program's Center for the Evaluation of Risk to Human Reproduction (NTP-CERHR). This review concluded with the finding the adults need not be concerned with exposure to BPA, but there is "some concern" with respect to the neurological effects of BPA on infants (NTP-CERHR 2008).

One might ask why the FDA relied upon the industry-funded studies that found no detrimental effects and did not weigh the results that showed a wide array of potential human health concerns. Some believe that it is due to the outdated standards that the government places upon scientific research it uses for risk assessment. The best studies,

according to the government, have a number of characteristics. For one, an experiment with a larger number of experimental subjects creates more reliable data. While it is true that larger sample sizes offer more statistical weight in terms of risk assessment, in many cases the only studies that have large populations are those that have a lot of funding. Typically, the only entities capable of supplying this amount of funding are industrial corporations. Publicly funded studies often do not have the resources to house, feed, and evaluate a large number of animals.

Another criticism is that the FDA did not consider many studies that did not exemplify Good Laboratory Practices (GLP) (FDASBS, 2008). To be considered as having GLP status a study must follow strict criteria set forth by FDA guidelines. However, in the case of BPA the few GLP studies that exist have flaws as noted by prominent researchers (Myers *et al*, 2009). Essentially they argue that a few pieces of flawed research are being accepted over a multitude of studies that show contrary results because they cannot reach the standards set forth by GLP guidelines because of funding issues.

In the case of BPA it seems almost as if the federal government is lagging behind state and local governments due to its adherence to traditional means of evaluating risks. An inherent failing of the US government is that industry is given the benefit of the doubt when introducing a new chemical into consumer products, the exception being food products and medical prescriptions which undergo assessment through the FDA. However, BPA is not intentionally placed into food products. It is in storage containers and cans, which are not heavily scrutinized. It was only recently discovered that BPA and other compounds in plastic can migrate into food products. In this circumstance, it is

up to scientists and NGOs to prove that the chemicals in the containers constitute a threat to human health.

To date the FDA has not yet released its revised assessment, though it has admitted to "some concern" with respect to BPA's effects on child development. In the meantime, a bill has been proposed to Congress by Senator Dianne Feinstein that proposes to ban the sale of food and beverage containers that contain BPA (Kissenger, 2009). Under the bill, any items containing BPA that have already been produced may still be sold. This is a very ambitious piece of legislation, and has met with a lot of resistance from the industrial sector and its supporters. It will not be surprising if the bill is redrafted to give some concessions to the plastics industry or if it is discarded outright because it is deemed too onerous to industry. However, if the bill does pass it will not only be an important step towards regulating BPA, but also to controlling other suspected environmental estrogens by setting a precedent for their regulation in consumer products.

The Price of Precaution

The debate over the regulation is full of ethical dilemmas. On the one hand plastics give us cheap, reusable containers for food and drink, and make up parts of vital health care equipment. On the other, exposing our entire population to a chemical that may be affecting us at the subcellular level, turning on metabolic processes that alter our development, could lead to a disastrous future. The government needs to consider all of these options fully before coming to a decision.

Precaution does have its costs. There will not be an overnight switch to plastic food containers and medical devices that do not contain BPA. However, recent research

has linked BPA to common health issues such as diabetes, obesity and heart disease (Lang *et al*, 2008). If this research is valid, many of these common maladies may be diminished, saving expenses on medical needs at the cost of controlling BPA. In this light, regulation appears that much more attractive.

Put in simpler terms, consider a dietary supplement. In pill form, it can provide the human body with various nutrients and vitamins that are needed for essential life functions. Now imagine a BPA supplement pill. We do not quite know how it will affect our bodies. We know that it is not a substance naturally found within our bodies. We know that in some cases it has effected growth and development, even our neurological functions. Some studies have even linked BPA with obesity and diabetes. Is this BPA supplement something we would voluntarily take, not quite knowing the outcome?

Regardless, ethical arguments will continue to be introduced and challenged by both sides. As we have seen in state policy arenas, ethical arguments on precaution have been winning to a great degree as regulations are established that prohibit the sale of baby bottles and other items for infants that contain BPA. In cases such as those, decision-makers will often look to other governmental entities that have already made a ruling on a particular issue. At the scale of the US federal government, this means examining the conclusions of other countries regarding the use of BPA.

Chapter 6 – BPA Worldwide

While the United States continues to debate the issue of BPA, the governments of other nations have already come to conclusions regarding the chemical. Japan, the European Union, and Canada have all reviewed the current science, evaluated the risks, and, in some cases, have taken steps to limit the amount of BPA circulating through their populations. It is important to consider the stances taken by these other nations, because their conclusions and subsequent actions can influence the final decision of US policymakers with regards to setting tighter controls on the proliferation of BPA.

Japan

Japan has had some of the earliest research and responses to the threat of BPA. Beginning in 1998, the Japanese government released several reports on the risks associated with exposure to BPA. Up until the release of the most recent report, each of the assessments concluded that further research was needed to fully quantify the risks associated with BPA. At the same time, these reports stated that there was no need for action to limit BPA exposure to the general population. Despite these conclusions, Japan has seen reductions in BPA use by industry arising from consumer actions.

The first Japanese risk assessment was completed in 1998. While the final conclusion stated that "no scientific evidence has been found to date which shows BPA released from polycarbonate plastics seriously affect human health," the report acknowledged that the potential risks associated with exposures to low doses of BPA need to be more fully explored (AIST, 2007). This was followed up by a 2001 report on the low dose phenomenon of BPA issued by the Japanese Ministry of Health, Labour and

Welfare (AIST, 2007). The report concluded that current low dose studies were not reproducible, and that concerns associated with low doses of BPA were most likely of no concern. However, as in the 1998 report, recommendations for further studies on low dose effects were suggested.

At the same time, Japanese industries voluntarily decreased the amount of BPA used in their products in response to consumer concern. One of the reduction methods included using different linings for canned beverages (AIST, 2007). Though the effects of BPA on the population at large had not yet been fully determined, this response showed a willingness of industry to decrease reliance upon a chemical, which before had been considered safe and acceptable. Japanese consumer pressure was able to change the behavior of some manufacturers, similar to the response of baby bottle and water bottle producers in the United States.

In 2002 the Japanese Ministry of Economy, Trade and Industry released its own report on the endocrine disruption characteristics of BPA. The report's conclusions echo those of the previous two risk assessments, stating that the current literature shows that BPA is unlikely to be a threat to human health. However, it states that since there are potential developmental and reproductive risks, further research should be pursued (AIST, 2007). Like the US's assessments to date, it tries to reassure the public that BPA is safe for its current use, but that more research is needed to be certain. Another report prepared by the Japanese Ministry of the Environment in 2004 found that there was no threat to human health from oral exposure based upon results from the 2002 and 2008 Tyl

studies. The toxicity value of 0.5 mg/kg/day, derived from the NOAEL of 5 mg/kg/day, provided a margin of exposure (MOE)[12] of 560 *u*g/kg/day (AIST, 2007).

Japan released its latest determination on BPA in 2007. As with the United States and the European Union, the Japanese risk assessment for BPA concluded that their current standards protect human health more than adequately. Their calculated margin of error is sufficient for all age populations, even those that were calculated to have the highest BPA intake. To their merit, the writers even considered the amount of BPA that might leech from plastic children's toys should they be chewed on. However, as with the US FDA assessment, the Japanese reports rely heavily upon the results of the 2002 Tyl study, which, to reiterate, was funded in part by the plastics industry.

In many ways, Japan has taken the most action to limit the amount of BPA intake in its population. Many beverage companies reformulated the plastics lining in their beverage containers. Japan is the only nation to have considered the potential leeching of BPA from plastic toys that young children often put in their mouths. In light of the lack of research at the time, Japan opted to exercise the precautionary principle and protect the public from the perceived threat of BPA. It is only recently that regulatory authorities have concluded that BPA probably is not a threat, but even so the door is left open for further review of the issue.

The European Union

Along with Japan, the European Union also released comprehensive reports on BPA long before the United States. They have evaluated BPA for carcinogenicity,

[12] A MOE value is calculated by dividing one of the above key toxicity values by predicted maximum exposure, and if the toxicity value is based on an animal study, the resulting quotient is further divided by 10.

mutagenicity, and acute toxicity, in addition to the low dose phenomenon. Their first comprehensive report was released in 2003 and included an in-depth assessment of all the literature at the time on the risks of BPA exposure to human health. This was followed up by an addendum in 2008 that included an evaluation of the risks to the environment due to BPA exposure. In the interim of these reports, the European Food Safety Authority (EFSA) released its own study on the risks of exposure due to food contact uses of BPA.

The European Union released its first broad determination on BPA in 2003. The report includes assessments for all types of exposure scenarios, including food contact applications, environmental exposures, and occupational exposure. It also began to examine the effects of BPA on the natural environment. With regards to consumers, the European Chemicals Bureau made two broad conclusions. The first was that there is a need for further information and testing regarding potential developmental effects from BPA exposure. Despite this determination, the report states that, "In relation to reproductive toxicity, a NOAEL of 50 mg/kg/day has been established in a multigenerational study for effects on fertility and on development (ECB, 2003)." The second conclusion with respect to consumers was that there was no need for additional testing or the need for additional precautions beyond what was already being taken for all other endpoints, such as carcinogenicity and mutagenicity.

To their credit, the 2003 EU assessment was very conservative in its exposure assessment to adults. At the time, there was a study that showed a very high concentration of BPA in wine due to the plastic lining found in wine casks. Since there was no other figure, the European Union used this number, 650 ug/L, despite the fact that

it was well above concentrations found in other products using an epoxy lining for storage the European Union determined that there was no risk to the health of adults. They also estimated that the average person consumes 0.75 liters of wine per day. However, even with the high dose estimate from wine consumption the European Union's total exposure estimate from consumption of food and drink products was only 600 ug/day. As previously stated, the report concluded that additional information is needed to accurately determine the developmental risks associated with BPA exposure. The ECB specifically identifies that it needs a 2-generation study in mice in order to fully evaluate the BPA for these effects.

The European Union's decision on BPA in food contact applications was brought into question in 2006. As a result, the EFSA formed a panel to re-address the issue. They concluded the following at that time:

> The Panel considered that low-dose effects of BPA in rodents have not been demonstrated in a robust and reproducible way, such that they could be used as pivotal studies for risk assessment. Moreover, the species differences in toxicokinetics, whereby BPA as parent compound is less bioavailable in humans than in rodents, raise considerable doubts about the relevance of any low-dose observations in rodents for humans. The likely high sensitivity of the mouse to oestrogens raises further doubts about the value of that particular species as a model for risk assessment of BPA in humans (EFSA, 2006).

Ultimately the Panel concluded that the 5 mg/kg/day NOAEL for food contact exposure established by the Scientific Committee on Food (SCF) in 2002 was still valid in light of literature generated between the releases of the two reports. Additionally, at the time the SCF had derived a Tolerable Daily Intake (TDI) of 0.01 mg/kg/day by applying a margin of safety factor of 500, 10 for interspecies differences, 10 for individual genetic differences, and 5 for uncertainty in the literature. The EFSA Panel, based upon their assessment that the literature had grown in the interim from 2002-2006, actually removed

the factor 5 from the margin of safety calculation, making their TDI 0.05 mg/kg/day (EFSA 2006). In light of the US NTP-CERHR concerns over neurological disorders at exposures of 0.01 mg/kg/day, this new TDI is unsettling. Furthermore, it appears that a draft copy of a 2006 report authored by Tyl impacted the EFSA Panel's decision on the reproductive effects of BPA. This 2006 draft study appears to be an early version of Tyl *et al*'s 2008 study, in which a two-generational BPA exposure study was performed on a specific type of mouse, also one of the two reports that influenced the US FDA's decision.

The European Union's most current assessment was released in April 2008, and essentially serves to update the assessment released in 2003. With respect to the conclusions of the 2003 report, the 2008 report claims to have addressed the need for more data regarding the developmental effects of BPA. The two-generation mouse study that was identified as necessary to making its determination was obtained and subsequently reviewed. This report, deemed "as the gold-standard, definitive study of the reproductive toxicity of BPA," is none other than a final draft version of the same Tyl *et al* study used in the draft US FDA and the 2006 EU EFSA reports. The EU assessment does, however, note that the Tyl study does not examine the potential low dose neurological effects of BPA exposure, as previously noted in this research. In its conclusion, however, the 2003 NOAEL of 50 mg/kg/day for reproductive toxicity is upheld. Additionally, the conclusions for risk to the consumer are updated and state that there is no need for additional information/testing, nor is there any need for any additional precautions beyond those already being taken for all endpoints, including reproductive toxicity (EA-CAU, 2008).

In comparison to the NTP-CERHR and Japanese reports, the European Union appears to have evaluated a similarly substantial body of literature when determining the risks related to BPA exposure. However, while the NTP-CERHR found that there is some health concerns related to BPA exposure, the European Union determined that there was no cause for concern. Typically the EU has been somewhat more progressive regarding other environmental and human health issues. For example, the EU has already taken firm stances against the growth and import of genetically-modified foods, not withstanding the fact that there has been mixed scientific results in that area as well.

Canada

Unlike the United States and the European Union, Canada has already taken steps to limit BPA use in certain plastic products. Ultimately, its conclusion caused the regulatory banning of BPA in baby bottles. Plastic bottles with BPA in them may no longer be manufactured, imported, or exported in Canada. As a nation, Canada has had the most vigorous regulatory response to BPA.

In August 2008 Health Canada released their assessment of BPA exposure via food packaging. Though Health Canada had reviewed the Tyl *et al* studies, they were very much influenced by the findings of the NTP-CERHR expert panel. Unlike the US FDA and EU regulatory bodies, Health Canada acknowledged the validity of the 2002 and 2008 Tyl studies but also noted that these studies did not adequately address neurological effects associated with low, chronic doses of BPA. Health Canada placed a large emphasis on the NTP-CERHR report when making its determination. In particular, they highlight 8 studies conducted on rats and mice that were given doses of BPA orally

and monitored for neurological reactions following exposure, either in the developing embryos or the birthed offspring. Each of the 8 studies appear in the NTP-CERHR report, and, more importantly, all of them demonstrate a neurological effect at levels below the NOAEL of 5 mg/kg/day set forth by the Tyl studies.

However, despite the conclusions of these studies, Health Canada states that the predicted estrogenic activity for BPA[13] in humans at an estimated ADI of 0.02 ug/kg/day is not likely to generate a response in human beings. Based upon their view of the overall weight of evidence, Health Canada concluded that there is no risk associated with the current amount of BPA to which the general population is exposed to, including infants and children. Regardless of this determination, the report concludes with the following assertions:

> …the neurodevelopmental and behavioural dataset in experimental animals, suggest a heightened sensitivity during stages of development in rodents…
>
> Although highly uncertain, these data sets suggest the need for more focused attention on products consumed by newborns and infants. It is therefore recommended that general principle of ALARA (as low as reasonably achievable) be applied to continue efforts on limiting BPA exposure from food packaging applications for this segment of the population (Health Canada August, 2008).

Even though other reports had already reviewed the effects of BPA on humans, Health Canada applied the precautionary principle because there is still scientific uncertainty regarding some of the low-dose effects of BPA. Due to this exercise of the precautionary principle, the Canadian government issued a ban on the use of BPA in baby bottles.

Looking forward, in 2008 Canada stated that it has already committed $1.7 million over the next 3 years for additional BPA research (Health Canada October, 2008).

[13] Estrogenic activity at this lower level was estimated by comparing the difference in effects between BPA and estradiol at higher concentrations and extrapolating the activity at 0.2 ug/kg/day.

In particular, Environment Canada plans to examine how BPA is making its way into the natural environment, and if there will be any potential harm caused to aquatic species.

Conclusions to be Drawn from the International Community

Based upon this review of regulatory recommendations and decisions of these three countries, it seems as if there is a fine dividing line between deciding whether BPA is perfectly safe in the amounts that consumers are currently exposed to or whether there is a need for more research before making a regulatory decision. On the other hand, Canada has already taken action precisely because the effects of exposure aren't fully known. One similarity between those agencies that declare that current acceptable BPA exposure levels are perfectly acceptable is the reliance on the 2002 and 2008 Tyl studies to provide a threshold value for human exposure. The regulatory bodies that dissent from this opinion both claim that the neurological effects have not been fully evaluated. Notwithstanding who is right and who is wrong at this point, research is still forthcoming on the effects of BPA on human beings.

Much of the existing research has varied results, with some studies reporting noticeable effects or positive correlations to BPA exposure and others showing no effects or no associations whatsoever. In light of this, the mere fact that there are studies showing health effects from concentrations of BPA that humans are reportedly exposed to everyday, which are above regulatory standards, should raise some concern in regulatory circles. Other than Canada, no other nation has applied the precautionary principle to BPA. Perhaps this is because BPA has been in use since the mid-20th century, and as such was introduced into the market when chemical screening protocols

were lax. Industry may be so reliant upon it that it would be a significant economic loss to change to a different compound. This may explain why the plastics industry is using any influence it has to confound scientific studies and swing regulatory agencies.

For the most part, at this time the majority of world governments are trying to take the wait and see approach. At the moment they conclude that there is no need for concern, but if the "weight of evidence" begins to point at a serious risk to the population action is likely to be taken. Though not the safest approach, it is deemed the most practical by most governments.

Chapter 7 – Assessing the Likelihood of Bisphenol A Regulation

The debate surrounding BPA is anything but clear. The pool of scientific literature continues to expand. Stakeholders continue to argue their positions. The federal government will have to make a concrete ruling one way or the other in time. The question is, which way will the ruling fall?

Historically, BPA has been known to have estrogenic effects for the greater part of a century. Despite this knowledge, it was introduced into food packing due to the convenience of production and its utility in a variety of applications under the belief that it would not migrate out of plastics in significant amounts. In the 1990s this was shown to be otherwise, and spurred the scientific community into investigating the matter more thoroughly.

Although there has been over a decade of research, the scientific arena has not yet reached a consensus on the relationship between BPA and the human body, and so regulatory authorities must decide if the weight of evidence is sufficient to promulgate restrictions. Some studies show negative effects on rodents at levels humans are exposed to on a daily basis; others similarly show negative effects, but at levels individuals likely aren't exposed to every day. And still others show no effects at any level affecting humans. While the majority of studies do show some effects, clearly it is not enough for the FDA to make a final decision. They have instead stated that they will continue to examine scientific studies, but have given no indication as to how long it will take them to make a decision.

In the wake of this scientific and regulatory uncertainty, the involved stakeholder groups make their ethical arguments in an attempt to steer any possible regulation of

BPA. The plastics industry urges the government not to make any unwarranted decisions that would entail a reformulation of a plastic that is stunningly ubiquitous in our society. Meanwhile, environmental NGOs argue that because of its prevalence and potential threat, we need to stop the use of BPA as soon as possible, regardless of the fact that there is no line of causality firmly established. In effect, they say that it is better to be safe than sorry. At the international level other nations have made official rulings on the fate of BPA. It may be that as further nations release their stances on BPA the United States will officially declare its position.

In light of all this information, is there a possibility for federal regulation of BPA in the United States? Cutting to the core of the matter, it is not the science that will be the deciding factor when considering federal regulation against BPA. Establishing a direct route of causality is nearly impossible, as it would be extremely unethical to dose humans with BPA in order to identify a negative response Furthermore, while longitudinal monitoring studies are beginning to be established, there is no possible way to have a control group because there are nearly zero populations which aren't exposed to BPA. However, as scientific evidence showing harmful effects builds up it can assist in tipping the scales towards more stringent regulation.

Rather, it is public concern over the risk to child development that will have the most influence on potential regulation, and to a degree the stakeholders who are pushing for stricter control of BPA are winning as we observe more and more state and local governments are continuing to ban the use of BPA in baby bottles. Still, at this point in time, it is unlikely that the FDA will ban BPA. However, with the increasing number of

state and local proposals to restrict BPA the possibility of a federal action by legislative means is a serious possibility.

If federal regulation is established, the question of how broad the restrictions will be will need to be considered. One option would be to ban the use of BPA in food containers outright. However, the use of BPA has grown along with the amount of food and beverage containers to the point where it is completely saturated the food industry. The manufacturers of personal water bottles and baby bottles have reformulated their plastic so it doesn't include BPA, but is this an option for other items? Japan was only able to reduce the amount of BPA in the epoxy linings of cans. Imagine if tomorrow the federal government introduced a regulation that utterly banned the use of BPA in any type of application. What would manufacturers do? Society would still want and need their products. Industry would have to reformulate can linings, containers, and a host of other products. Would the replacement chemical be easily substituted into the manufacturing processes? Or would it require an overhaul of existing production lines to accommodate the new chemical? Would distributors still be able to sell products containing BPA, or would those products need to be thrown out? Do we gradually shift from BPA to a new chemical? Is this chemical safe? Is it safer as compared to BPA?

In light of all these questions, it can be said that the United States would not introduce an outright ban of BPA. It would take an exceedingly strong scientific report or reports that proved indisputably that BPA is a serious threat to human health. Instead, what we will likely see is the same regulations being established on state and local levels. These restrictions are most likely to be put forth in a legislative action, such as the one proposed by Senator Feinstein.

With the recent national elections, conservatives have obtained a majority in the House of Representatives. This may mean that Feinstein's proposal will get blocked. Additionally, it is quite possible that Feinstein's proposed bill will be ignored in the light of other matters that take up more of the public's attention, such as the burgeoning economic woes and the continued debate over healthcare reform. These occurrences make the likelihood of successful federal legislation slim.

However, state and local governments are continuing to place bans upon certain uses of BPA. If this continues at its current rate, individuals in communities that don't have these restrictions will begin to question why these safeguards aren't in place for them. Once this critical level is reached, the federal government will almost be forced to ban BPA in baby bottles lest it look like it does not care for its future constituents.

With respect to the evidence I have presented and the arguments I have made, I conclude that the United States will likely implement a ban on BPA. It will not be a comprehensive ban. Rather, it will follow what the Canadian, state and local governments have done and ban BPA-containing products for infants. It cannot be determined if this will encompass all baby products, including items such as teething rings that infants might put in their mouths, or if it will only cover baby bottles and perhaps formula containers. Additionally, it cannot be determined how long it will take before the federal government decides to act. However, based upon the ethical argument of safeguarding our children and the trend of lower levels of government, representatives at the federal level will more than likely follow suit.

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