INTRODUCTION

Plastics are an omnipresent part of the world today, and they date as far back as 1600 B.C. when rubber was shaped by human hands and polymerized. Since that time, plastics have evolved quite a bit and came into mass production in the 1940s (Halden 2010). Today, there are over twenty different kinds of plastics, and the plastic industry is a multi-million-dollar business. Since plastics are such a ubiquitous part of life, people are exposed to plastics every day in many forms, including food and drinking products, bathing products, medical products, and many others (Halden 2010). This abundant exposure to plastic in recent years has been correlated with various health issues, and this review will examine two ingredients of plastic that have been linked to breast cancer in particular: bisphenol A (BPA) and phthalates.

Bisphenol A was first synthesized in 1891 and is a building block of polycarbonate plastics. BPA is widely used in food containers including Tupperware, food contact paper, metal food cans, and baby bottles. BPA can also be found in thermal papers, dental materials, PVC pipes, medical devices, and personal care products (Wang et al. 2017). Phthalates have been produced in large quantities since the 1930s and are diesters of phthalic acid. Phthalates are incorporated into plastics as plasticizers to create flexibility, pliability, and elasticity in normally rigid plastic polymers (Halden 2010). Phthalates can be found in industrial plastics, paints, medical devices, children’s toys, and personal care products like sunscreen and perfume (Halden 2010). Of the two plastic ingredients, BPA is produced in higher abundance annually than Phthalates, 9 million tons to 8 million tons, respectively (Gerona et al. 2020; Wang et al. 2019). Most of the BPA and phthalates produced stays in its product, but some of the BPA and phthalates will enter the body through ingestion, inhalation, and dermally. When these chemicals enter the body, they can act as endocrine disruptors which impact the function of the body’s endocrine system. When the endocrine system is disrupted, many adverse health effects can follow, including carcinogenesis. A type of cancer that is particular susceptible to endocrine disruption is breast cancer.

Breast cancer is the most common cancer diagnosis for U.S. women, excluding skin cancers, and is the second-leading cause of cancer death for women after lung cancer. Between the years 2012 and 2016, the incidence rate of breast cancer increased by 0.3% per year (Desantis 2019). These statistics show the destructiveness of this disease, and it is possible that a contributing factor could be found in everyday products including foods, drinks, cosmetics, toys, and anything that contains BPA and phthalates. The objective of this review is to examine the current literature for the potential effects of BPA and phthalates on the development of breast cancer. This review also explores some of the possible mechanisms of how phthalates and BPA have carcinogenic effects on human mammary glands.

REFERENCE DOSES

In the last thirty years, scientists have realized that plastics could have a harmful effect on human health. Therefore, scientists conducted research studies to create a reference dose for both BPA and phthalates. A reference dose is the amount of a certain product someone can absorb into their body daily without a harmful effect later in life. The reference dose for BPA and phthalates are 50 g/kg and 20 g/kg respectively (Wang et al. 2017; Benjamin et al. 2017). Most of the research done to create these reference doses was created using indirect urinalysis, which estimates the amount of BPA in the body by examining the second or third metabolite into which BPA is broken down in the urine (Gerona et al. 2020). Since the early 2000s, there has been a new direct form of measuring BPA in the urine that examines the first metabolite into which BPA is broken down, and when this direct form of urinalysis is used, the results can differ greatly from the indirect urinalysis results. A recent study published at the end of 2019 showed that BPA levels were 44 times higher using the direct method instead of the indirect method which has been used for the bulk of research on BPA (Gerona et al. 2020). This study specifically examined the difference in direct and indirect urinalysis in BPA, but a
large portion of phthalate research on humans has been done using an indirect method of urinalysis, so there is a need for a direct method of urinalysis in phthalate research as well (Gerona et al. 2020). This study confirms that there is a need for reference doses to be reevaluated using modern data collection techniques, and this is a cause for concern because people may have put themselves at risk due to a possibly inaccurate reference dose.

SOURCES AND ROUTES OF EXPOSURE FOR HUMANS

Since plastics are such an omnipresent part of life, the routes of exposure for BPA and phthalates are plentiful. The three main ways that BPA and phthalates enter the body are ingestion, dermal exposure, and inhalation. The most prevalent way is through ingestion. The European Food Safety authority showed that the dietary daily amount of BPA exposure for infants was on average 0.2-13 g/kg and 1.5 g/kg for adults (Wang et al. 2017). Another study showed that estimated exposure of BPA through inhalation was 0.00024-0.00041 g/kg, and the estimated dermal exposure was 7.1-42.6 g/kg (Wang et al. 2017). Table 1 can be referred to for the specific ways in which BPA enter the body including plastic bottles, air, contaminated seafood, and dental materials.

Table 1. Routes of exposure for BPA in daily life. This table displays some of the possible ways that BPA can enter human’s bodies and the concentrations that BPA was found in these routes of exposure. These concentrations are raw amounts, and the actual amount entering the human body is much less.

<table>
<thead>
<tr>
<th>Contamination sources</th>
<th>BPA concentrations</th>
<th>Exposure routes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic environment</td>
<td>Up to 56 µg L⁻¹</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Soil</td>
<td>1–150 µg kg⁻¹</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Landfill leachates</td>
<td>Up to 17.2 mg L⁻¹</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Air</td>
<td>2–208 ng m⁻³</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Dust</td>
<td>0.2–17.6 µg g⁻¹</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Contaminated seafood</td>
<td>13.3–231.1 µg kg⁻¹</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Metal food cans</td>
<td>2–82 ng g⁻¹</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Plastic bottles</td>
<td>0.234 µg g⁻¹</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Temporary paper</td>
<td>7.1–17 µg day⁻¹</td>
<td>Dermal route</td>
</tr>
<tr>
<td>Dermal materials</td>
<td>0.013–36 mg day⁻¹</td>
<td>Dermal route</td>
</tr>
</tbody>
</table>

The average amount of phthalate exposure through ingestion is between 1.854-3.209 g/kg daily. The average amount of dermal exposure for phthalates is 0.010–0.016 g/kg and the average inhalation exposure is .004686-.945 g/kg daily (Giulivo et al. 2016). The specific mediums that allow the phthalates to enter the body can be seen in Table 2 and include bottled water, personal care products, and fish (Giulivo et al. 2016).

Table 2. Routes of exposure for phthalates in daily life. This table displays the routes and concentrations via which humans could be exposed to phthalates.

<table>
<thead>
<tr>
<th>Routes of exposure</th>
<th>Concentrations</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>10⁻³ to 10⁻⁷</td>
<td>Dermal</td>
</tr>
<tr>
<td>Air</td>
<td>0.001 to 0.01</td>
<td>Dermal</td>
</tr>
<tr>
<td>Soil</td>
<td>0.12 to 0.3</td>
<td>Nasal</td>
</tr>
<tr>
<td>Contaminated water</td>
<td>10⁻² to 10⁻¹</td>
<td>Oral</td>
</tr>
<tr>
<td>Food</td>
<td>10⁻² to 10⁻¹</td>
<td>Oral</td>
</tr>
</tbody>
</table>

It is important to understand the routes of exposure for BPA and phthalates in order to understand how these chemicals can enter the body and cause carcinogenesis. It is also important to understand the average daily exposure to BPA and phthalates because the mechanistic studies try to mimic these concentrations in their experiments.

EPIDEMIOLOGICAL EVIDENCE OF BREAST CANCER

Epidemiological studies have found a link between breast cancer and the plastic components BPA and phthalates. A study done in 2010 on a group of 454 women found that diethyl phthalate (DEP), which is type of phthalate, is significantly associated with breast cancer in premenopausal women. It also found the phthalates benzyl butyl phthalate (BBzP) and dioctyl phthalate (DOP) were found to be inversely associated with breast cancer (López-Carrillo et al. 2010). Another study done in 2017 showed a significant association between di-2-ethylhexyl phthalate (DHEP) and breast cancer (Zuccarello et al. 2018). All of the phthalates just discussed all have the same general structure of a benzene ring with two ester groups, but the variability comes from the R-groups attached to the esters. It is also significant to note that the mean phthalate levels in the study done in 2010 were 0.174 µg/kg which is greatly below the reference dose, yet there was a significant association with breast cancer (López-Carrillo et al. 2010). Another epidemiological study involving BPA and phthalates found that breast density was elevated by 5% in women with BPA or phthalate levels above the median detected value compared to women with undetectable levels. Increased breast density is a risk factor for breast cancer, and a previous study suggests that a 5% increase in breast density increases breast cancer occurrence by 5-10% (Sprague 2013). Another study done on both BPA and phthalates showed that the chances of a woman developing breast cancer were doubled in women who manufactured BPA and phthalates.
(Brophy et al. 2012). These epidemiological studies are significant because they prove that phthalates and BPA can cause breast cancer in vivo. Even though the mechanism of how BPA and phthalates cause breast cancer have only been demonstrated in vitro, these epidemiological studies are proof that some mechanism is occurring in vivo, but more research is needed to uncover it. It has been proven that there is an association between the plastic components BPA and phthalates and breast cancer. Several studies have also identified the routes of exposure for these two plastic components and the BPA and phthalates doses to which humans are exposed. The next logical step in the investigation of these chemicals is to determine the mechanism of how these chemicals cause breast cancer. As stated earlier, the mechanisms have not been determined in vivo, but there are several in vitro mechanisms that have been discovered, including the c-myc, ERK1/2/ERRy, VEGF, AhR/HDAC6/c-myc, and PI3K/ATK pathways.

MECHANISMS OF HOW BPA AND PHTHALATES CAUSE BREAST CANCER

There are millions of genes in the body and they all have a specific function in making sure the body is running smoothly. However, there are certain genes known as oncogenes, genes that have the capability to cause cancer if they are mutated in a certain way, and it has been found that BPA and phthalates have the capability to cause mutations to oncogenes and cause them to produce tumors.

One oncogene specifically is c-myc, an important gene in the cell cycle. C-myc promotes expression of cyclin D and CDK4 which hypophosphorylates pRb. pRb inhibits E2F1, and E2F1 is key in moving past the R-point. The R-point is in the G1 phase of the cell cycle and the R-point is the deciding point where a cell will begin to copy its DNA and proliferate or not. Once a cell moves past the R-point, it must proliferate. Once c-myc promotes expression of cyclin D, this causes an increase in cyclin E production which further phosphorylates pRb, allowing E2F1 to be released from pRb and expressed. E2F1 uses a positive feedback mechanism by producing more cyclin E, therefore pushing the cell past the R-point. The body has a normal level of c-myc production that allows for normal proliferation of cells. However, it was found that 10nM of BPA significantly increased the level of c-myc in breast cells (Pfeifer et al. 2015). This dose of 10nM of BPA is comparable to the dose to which humans are exposed because the average adult weighing 62kg and containing 5 liters of blood is exposed to 81.48 nM of BPA daily (Quilty-Harper 2012). If c-myc is overexpressed, then cells are pushing past the R-point way more often than normal, causing excessive proliferation and the possibility of tumor formation. Overexpression of c-myc can also shut down inhibitors like p-27 and p-15 which have the ability to halt the cell cycle and stop the excessive proliferation.

C-myc was also associated with an increase in production of reactive oxygen species which can lead to DNA damage. C-myc does this by allowing the expression of E2F1 which inhibits the transcription factor NF-kB. Normally NF-kB activates the antioxidant MnSOD, which helps reduce reactive oxygen species. Therefore, if c-myc is overexpressed, then there will be fewer antioxidants and more reactive oxygen species damaging DNA (Pelengaris and Khan 2003). DNA damage can lead to carcinogenesis in hundreds of different ways, including putting a gene that increases motility under a new promoter or by destroying genes that normally cause cell apoptosis.

Phthalates can also cause the overexpression of the oncogene c-myc which increases the incidence of breast cancer. In the study linking BPA to overexpression of c-myc, a mechanism to how c-myc was overexpressed was not found; however, in the study on phthalates it was found that c-myc was overexpressed by the ahR/HDAC6/c-myc pathway. This pathway starts when phthalates cause AhR to translocate to the cell membrane and activate cAMP-PKA-CREB 1 signal cascade. cAMP activates PKA which phosphorylates CREB 1 at serine 133. CREB-1 is transcriptional factor that promotes the expression of HDAC6. HDAC-6, in turn, helps with the assembly of the B-catenin- LEF1/TCF4 transcriptional complex which expresses c-myc (Hsish et al. 2012). As stated earlier, c-myc increases cell proliferation by modulating the cell cycle and allowing it to move past the R-point. The overexpression of c-myc is caused by both BPA and phthalates which can increase the incidence of breast cancer.

Another mechanism of how BPA can cause breast cancer is the ERK1/2/EER pathway. A study initially found that 1nM and 100nM of BPA significantly promoted the proliferation of MCF-7 and SkBr3 cancer cells, so researchers investigated how the proliferation was occurring.
They found it was occurring through the ERK1/2/EER pathway. The mechanism begins with ERK1/2 being activated. ERK1/2 are kinases that phosphorylate DNA, RNA, and other proteins in normal cell proliferation and growth (Song et al. 2015). However, BPA can cause the ERK1/2 to malfunction and phosphorylate serine residues 51,81, and 219 on the ERR receptor which prevents it from ubiquitination (Heckler et al. 2015). Normally ERR receptor levels are kept in balance by ubiquination, but if this cannot happen due to certain serine residues being phosphorylated, then there will be more ERR receptors than normal (Heckler et al. 2015). ERR receptors have a structure similar to that of ERR receptors, and they are both endocrine-related receptors which play a role in normal mitochondria production and function; however, they can be taken advantage of by cancer cells to produce extra mitochondria for energy (Heckler et al. 2015; Song et al. 2015). Therefore, having more ERR receptors allows cells to proliferate more rapidly because they are supplied with the excessive metabolic needs of rapidly proliferating cancer cells.

Another common carcinogenic pathway that has been discovered to be caused by phthalates is the PI3K/AKT pathway. The PI3K/AKT pathway mediates the effects of a variety of extracellular signals in various different cellular processes, including cell growth, proliferation, and survival. When these cellular processes are mutated and modified, they can lead to tumor formation. A study done in 2014 demonstrated that concentrations of phthalates between 10nM and 1000nM can induce cell proliferation, and these concentrations were associated with significantly higher levels of PI3K and AKT (Chen and Chien 2014). The mechanism behind this pathway is that PI3K is a kinase that phosphorylates PIP2 to PIP3 which then recruits AKT to the cell membrane and activates it. The activated AKT inhibits GSK3B. Normally, GSK3B degrades myc and cyclin D which stop the cell cycle. However, if GSK3B is inhibited by elevated AKT levels, then proliferation can be increased. AKT also inhibits "BAD" which is a pro-apoptotic protein that is turned on when the cell is damaged beyond repair to stop mutated cells from continuing to proliferate. If BAD cannot be turned on, this allows tumorigenic cells to continue to replicate.

The last mechanism of carcinogenesis involves VEGF. VEGF normally helps in the formation of new blood vessels during embryonic development and during the wound healing process. However, both phthalates and BPA can cause elevated VEGF levels. The results of a study on two breast cell lines showed that 1000 nM doses of phthalates and BPA significantly increased VEGF secretion by the breast cells. If VEGF is being produced in abundance, this allows the cells that are proliferating at a high rate to produce more blood vessels in order to supply the cells with extra nutrients (Buteau-Lozano et al. 2008). As cancer cells proliferate and a tumor begins to form, the cells begin to move away from the blood supply, but if high levels of VEGF are present, new blood vessels can form near the new cells away from the normal blood supply. This is essential step in the carcinogenesis of breast cancer cells.

The above mechanisms of how BPA and phthalates cause breast cancer are just a few of the prominent ones that have been discovered so far. There are more mechanisms in the literature, and more will continue to be uncovered. It is also notable that these mechanisms may not be occurring exclusively, and that a few of these mechanisms may be working at the same time in order for tumorigenesis to occur. All of the mechanisms above cause proliferation of cells, but they differ in how they help with proliferation. The c-myc mechanism helps the cells replicate DNA, the VEGF mechanisms helps the proliferating cells continue to move away from the normal blood supply, and the EER pathway helps with the energetic needs of proliferating cells. All of these mechanisms work towards the common goal of tumorigenesis.

CONCLUSION

This review examined the current literature on the potential effects of BPA and phthalates on the development of breast cancer and explored some of the mechanisms that BPA and phthalates use in carcinogenesis. Epidemiological studies done on BPA and phthalates prove there is a link between BPA, phthalates, and breast cancer. Moreover, the routes in which BPA and phthalates enter the human body have been discovered. However, the dosage at which BPA and phthalates are safe to absorb inside the human body needs more examination based on updates in urinalysis and recent research. Also, further longitudinal studies are needed on the effects of BPA and phthalates because all of the epidemiological studies have been completed using a cross-sectional method. Some of the
mechanisms behind BPA and phthalate breast cancer carcinogenesis have been discovered in vitro, including the c-myc, ERK1/2/ERRγ, VEGF, AhR/HDAC6/c-myc, and PI3K/ATK pathways, yet these mechanisms have not been examined in vivo. Therefore, there is more research needed to uncover new mechanisms of BPA and phthalate carcinogenesis and to figure out if these mechanisms occur in vivo. BPA and phthalates have only been around for roughly a century and only in the past few decades have scientist begun to dive into the effects of these plastic components on human health. There is still an abundance of research to be conducted on BPA and phthalates in order to fully understand their effects on human health, specifically on their link to breast cancer.

REFERENCES


The citation system used in this essay is CSE 8th, Name-Year.