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Understanding the Effects of Phthalate Exposure

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ABBREVIATIONS AND ACRONYMS

DEHP	**di(2-ethylhexyl) phthalate**
DEP	**diethyl phthalate**
PVC	**polyvinyl chloride**
DINP	**diisononyl phthalate**
DIDP	**di-isodecyl phthalate**
DnOP	**di-n-octyl phthalate**
BBP/BzBP	**benzyl butyl phthalate**
DEHT	**dioctyl terephthalate**
CPAP	**continuous positive airway pressure**
IV	**intravenous**
DMP	**dimethyl phthalate**
DBP.	**dibutyl phthalate**

Abstract

Phthalates are found in nearly all everyday products; therefore, human exposure is inevitable. Phthalates are groups of chemicals classified as plasticizers that help increase the durability and shelf life of whatever product they are put into. The effects of phthalates can occur prenatally and throughout adulthood. Despite phthalates being understood to be endocrine disruptors, chemicals that block hormones and certain receptors, phthalate use within plastics is increasing every year- raising concern to find different alternatives. This research analysis will aim to define and explain what phthalates are and where they are found along with the harmful effects that occur due to exposure.

Understanding the Consequences of Phthalate Exposure

What are the true consequences of phthalate exposure? Phthalates are a group of chemicals, most commonly used as plasticizers in a multitude of products. To understand the sheer amount of phthalate exposure, one must realize how prevalent phthalates are. Phthalates are frequently found in: vinyl flooring, lubricating oils, plastic packaging, medical tubing, and personal care products, including but not limited to shampoo, soap, and hair spray (Centers for Disease Control and Prevention, 2021). Due to the large presence of phthalates, exposure is inevitable- regardless of whatever lifestyle changes an individual might make to lessen their presence. Recent research is revealing the negative side effects that occur with prolonged phthalate exposure. Given that phthalates are known endocrine disruptors, all negative consequences begin at a level that is not seen explicitly seen with the human eye. This paper will explain what phthalates are, their modes of exposure, and the specific effects that occur with exposure.

Define Phthalates

In 2022, the world emphasizes a healthier lifestyle, however, there is a tiny non-visible chemical that is potentially preventing that- phthalates. Phthalates are found in virtually everything, from vinyl flooring to personal care products to almost all plastics. Phthalates were first developed in the last century, aiming to extend the expiration date of whatever product they were put in (Marin Breast Cancer Watch, n.d.). Phthalates were originally introduced in the 1920s, and by 1931 phthalates a large component of polyvinylchloride production, PVC (Cambridge Isotope Laboratories, INC, 2015). During the production of PVC, specific phthalates are added to the PVC resin- allowing for customization to which ever product it becomes. Polyvinylchloride is often found in medical devices, flooring, footwear, insulation, water service pipes, and a multitude of other commonly used items. Phthalates are created by reacting phthalic anhydride with an alcohol (Cambridge Isotope Laboratories, INC, 2015). The formula for all phthalates are $C_nH_nO_n$, the higher the number of carbon atoms within the backbone, the increased durability and permanence of phthalates. Figure 1 shows the names and chemical structures of commonly used phthalates used in industry including "high" phthalates such as diisonynyl phthalates (DINP) and diisodecyl phthalates (DIDP).

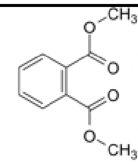
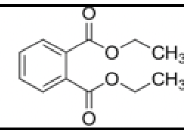
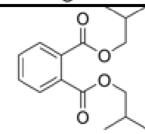
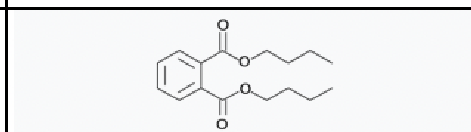
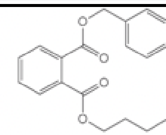
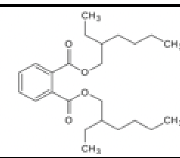
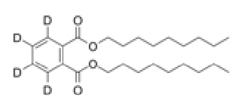
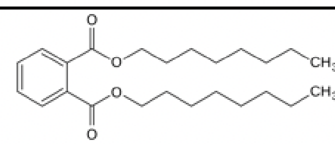
Phthalate Ester	Chemical Structure
Dimethyl Phthalate (DMP)	
Diethyl Phthalate (DEP)	
Di-iso-butyl Phthalate (DiBP)	
Di-n-Butyl Phthalate (DBP)	
Butyl Benzyl Phthalate (BBP)	
Di(2-Ethylhexyl) Phthalate (DEH)	
Di-n-Nonyl Phthalate (DnNP)	
Di-n-Octyl Phthalate (DnOP)	

Figure 1: Lists common phthalates along with their abbreviation and chemical structure

The majority of individuals associate phthalates with plastic products however phthalates are not chemically bonded to plastic but physically bonded, essentially the phthalates are "stuck" on the surface of plastics which allows them to be easily removed from the product material. Phthalates are also present in a variety of personal care products including: nail polish, perfumes, deodorant, hair gel, shampoo, soap, hair spray, and body lotion- this is to help maintain the fragrance and lubrication of these substances (Marin Breast Cancer Watch, n.d.). These sources expose humans to the compounds through direct bodily contact through absorption or ingestion. In all cases, the primary use of phthalates is to help increase durability and longevity of products, and flexibility of plastic products. The major issue that arises with phthalates in human exposure is that they are endocrine disruptors. The endocrine system is made up of hormones that are used regulate all biological processes that occur from conception throughout adulthood and into seniority (Cleveland Clinic, 2020). Major parts of the endocrine system include the ovaries, testes, the pituitary gland, thyroid gland, and adrenal glands. The effect on the endocrine system by phthalates will be discussed extensively throughout the remainder of the paper.

Identify Phthalates and Phthalate Exposure

The six most prevalent phthalates in consumer products are di-(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), dibutyl phthalate (DBP), diisodecyl phthalate (DIDP), di-n-octyl phthalate (DnOP), and benzyl phthalate (BBP/BzBP). DEHP, BBP, and DINP are the phthalates with the most anti-androgenic properties. An anti-androgenic substance prevents androgens (male sex hormones) from binding to their respective receptors which can cause endocrine disruption (National Cancer Institute). Anti-androgenic properties are just the beginning of the harmful effects that follow with the use of phthalates. Di-(2-ethylhexyl) phthalate, DEHP, is the most widely used phthalate, mainly as a plasticizer seen in PVC (Barakat et al., 2018). The main metabolite of DEHP is mono-(2-ethylhexyl) phthalate (MEHP) which is increasingly more bioactive than DEHP. It has been noted that prenatal DEHP exposure in mice leads to reduced ovarian weight and increased uterine weight (Barakat et al., 2018). Prenatal exposure to DEHP in humans leads to increase uterine weight, decreased anogenital distance, disrupted cyclicity, and reduced fertility (Barkat et al., 2018). This prenatal exposure to phthalates has drastic consequences, coupled with decades of exposure through family lines, the effects of phthalate exposure can be seen across generations. Specific effects of prenatal exposure will be discussed in greater detail in this paper. Compared to other phthalates, MEHP is responsible for more pathological alterations that occur within the body. BBP, which is widely phased out due to health issues, was originally used in adhesives and sealants, floor coverings, paint, and plastic/rubber products (United States Environmental Protection Agency, 2022). BBP, or butyl benzyl phthalate, is an oily liquid additive used to enhance the flexibility of plastics. BBP is amongst the prohibited chemicals listed on California's Proposition 65, other phthalates listed include: DBP due to female and male developmental concerns, DEHP due to male developmental concerns and cancer concerns, DnHP due to female and male concerns, DIDP due to developmental concerns, and DINP due to cancer concerns. California's Proposition 65 requires businesses to inform citizens about significant exposure to chemicals that are linked to cause cancer and reproductive harm (California Office of Environmental Health Hazard Assessment, n.d.). DINP, diisononyl phthalate, is a plasticizer often used in vinyl flooring, cable insulation, coated fabrics, artificial leather, rubber inks, and pigments/paints (Vermont Department of Health, 2018). It should be noted that most products use a combination of phthalates, not a single phthalate. DINP, like other phthalates, has anti-androgenic effects, combining these effects with other anti-androgenic phthalates can create extremely harmful effects, including but not limited to reproductive harm and potential terminated pregnancy. Mono-(carboxyoctyl) phthalate, which is a metabolite of DINP, has been calculated to be present

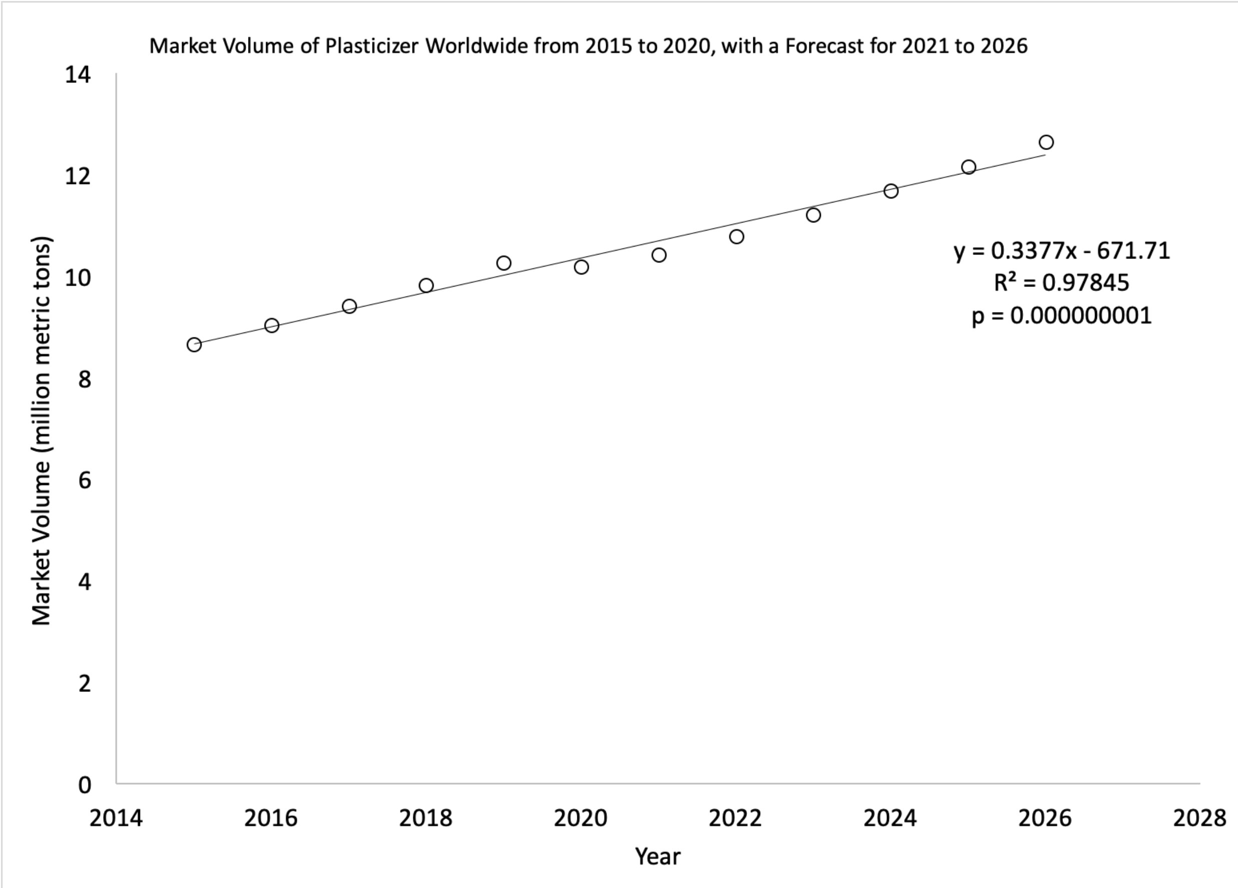


Figure 2: Data gathered from Statista, regarding the market volume of plasticizer use from 2015 through 2023. A regression analysis was performed in order to determine statistical significance.

within 95.2% of the U.S. population, sampled. How exposure to phthalates occurs will be discussed further into this analysis, however the mentioned percentage gives a glimpse into how prominent these toxicants are in everyday life. Despite the known negative effects of phthalates, global plasticizer use is steadily increasing every year (Fernandez, 2022). Figure 2 depicts worldwide data regarding plasticizer use, even forecasting into 2030. With such a strong correlation coefficient and such a small p-value, the increasing market volume of plasticizers is extremely prevalent.

Whereas it is common for specific chemical exposure to only occurs through one route, via ingestion or skin contact, phthalate exposure can occur via multiple modes: ingestion, inhalation, or skin contact (Wang and Qian, 2021). The type of exposure can lead to developmental and reproductive disruption. Once phthalates exposure occurs and enters the body, they rapidly transform into the respective toxic metabolites. Certain metabolites are made up of functional groups that can be chemically reactive and have the potential to modify or react with DNA and proteins within the body that can result in cellular toxicity such is the case with DEHP (Rowdhwal and Chen, 2018). Depending on the product, certain plastics contain up to 40% of phthalates by weight- there really is no avoiding the presence of these toxins (Thomson, 2009). Figure 3 depicts the variety of ways phthalate exposure can occur on a pregnant individual along with a potential effect.

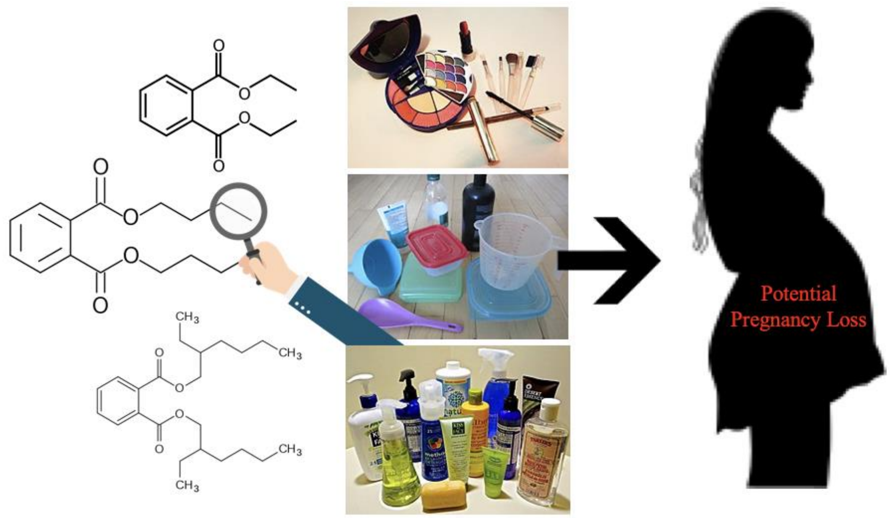


Figure 3: Phthalates found in various cosmetics, plastic products, and personal care products could potentially lead to premature pregnancy loss. Image derived from Liao et al. (2018).

Within the food industry, phthalates are found in plastic packaging materials, most harmfully seen in microwavable meals. An unfortunate reality of phthalates is that they are not covalently bound to the material they are part of therefore they can migrate into food, the air, or onto the skin. The five most common phthalates used in the food industry are DEHP, DBP, BBP, DINP, and DIDP- with DEHP, DBP, and BBP being recognized as the most toxic. Specifically, fast food is associated with biomarkers of phthalate exposure (Edwards et al., 2022). DEHT was found at the highest concentrations in hamburgers, fries, chicken nuggets, chicken burritos, and cheese pizza, all from fast food restaurants. Of the food, cheese pizza had the lowest levels of phthalates. The presence of phthalates in fast food can be related to packaging of the food and even food handling. If fast-food is handled gloves containing phthalates, the chances of exposure are increased. In America, between 2013 and 2016, 36.6% of adults consumed fast food everyday (Fryar et al., 2018). This is not taking into account individuals under 18 and the expansion of the fast-food industry into 2022. Considering how much plastic is used to package and store and reheat fast food, phthalate exposure in the fast-food industry is extremely high. To further the point, between 2013 and 2016, it can be assumed that 36.6% of American adults were being exposed to phthalates every single day (Fryar et al., 2018). Given how common phthalates are in everyday products- electronics, personal care products, pharmaceuticals, etc., it is extremely concerning how debilitating their effects are. The main route of exposure to phthalates is due to ingestion of contaminated foods or dust particles (Boberg, 2018). While a majority of food packages are heated up and expedite the release of phthalates into food and therefore into humans, they could be avoided, however the presence of them in consumer and building products means they are constantly present in the indoor environment. In areas where vinyl flooring is common, phthalates are constantly released into the indoor environment. As previously mentioned, the easy release of phthalates is due to them not being tightly bound within the polymer matrix (Wu et al., 2017). A polymer matrix, or a polymer matrix composite, is the continuous phase in the composite that is used to keep the reinforcing agent within its place. Adding phthalates into this continuous phase gives that durability that makes plastic so useful. Despite the extreme emphasis on recycling, plastic still ends up in landfills. In 2020, 6.3 billion metric tons out of the 8.3 billion metric tons of waste, was plastic waste; approximately

79% (Asad, 2021). Due to the easy release of phthalates, they are often found in high concentrations within landfills. Over 2015- 2016, phthalate diesters were detected in all samples taken from five municipal landfills within Europe (Wowkonowicz & Kijenska, 2017). Therefore, once phthalate rich products enter landfills and sit there forever, phthalates become a ubiquitous with environmental contaminant. With this in mind, no matter how hard an individual may try to remove phthalate rich products from their lives, they are still inhaling the compounds through airflow and pollution. Once consumed, whether via the mouth, skin, or nose, phthalates are rapidly metabolized. Phthalate metabolism occurs within liver, gut, and blood, performed by esterase and lipases (Frederiksen, Skakkebaek, & Andersson, 2007). Esterase is an enzyme that hydrolyzes esters into acids and alcohol within a solution. Lipases are enzymes that hydrolyze fats within emulsion, specifically fats within foods while they are in the intestines. Depending where in the body the phthalates are getting metabolized in the body, depends which enzyme is at work. As previously mentioned, depending on the functional groups within the metabolite, potential toxic effects may occur.

Models of Phthalate Exposure

Research has been performed to understand various models of phthalate exposure. Wu et al. (2021) used *in vitro* and *in silico* studies in order to understand population-scale risks due to phthalate exposures. The in vitro and in silico techniques allowed for local sensitivity analysis to be performed and determined that there was no overlap in bioactivity of phthalate exposure in *in vitro* but was present in *in silico*. Using both *in vitro* and *in silico* techniques allow researchers to understand multi-route exposures that can be related to phthalate concentrations, specific chemical properties, and human activities. Understanding human activities is a major point in understanding phthalate sources of exposure.

Epidemiological studies of phthalate exposure revealed potential negative effects that can occur within the airway, nasal, ocular, and dermal allergic diseases (Bolling et al., 2020). Asthma, rhino-conjunctivitis and eczema have all seen correlations to phthalate exposure, however greater experimental studies need to be done to determine an exact relationship. In studies performed on rodents, phthalates can behave as adjuvants in levels due to environmental exposure, especially increasing respiratory and inflammatory effects due to allergens (Jaakkola & Knight, 2008). Simply put, if an individual is allergic to pollen, the presence of phthalates combined with pollen can increase the presence of symptoms. Along with physical symptoms, phthalates can also alter innate and adaptive immune cells (Hansen et al., 2015). Innate immune cells are white blood cells that mediate innate immunity, immunity that occurs at birth. Adaptive immune cells are lymphocytes/ T cells and occur after infection. Using cell cultures, research can combine multiple variables along with phthalate exposure in order to understand how working in collaboration may affect human populations. Phthalate exposure can influence cytokine secretion from macrophages and T cells via cellular signal pathways (Hansen et al., 2015). Metabolized DEP and DnBP were noted to disrupt the pathways that govern cytokine production.

Rats and mice are perfect models to use during research, especially in research around the endocrine given the similarities between them and human bodies. Islets of Langerhans cells in the pancreas of mice are relatively comparable to the same size in humans, allowing them to be perfect model organisms (Dolensek et al., 2015). Mice are the most studied animal exact mechanics of mice, especially how chemicals affect their body allows that information to indicate at how the same chemical may affect humans. It is hard to imagine, but regardless of their size difference, mice and humans have relatively similar organ systems and chemicals affect mice similarly to the way they affect humans. Using *in vitro*- and *in silico*- studies allows for tight control of chemical review and is relatively cheap (Graudejus et al., 2018). This is particularly helpful in understanding phthalate exposure because it allows research to test each individual phthalate at a time, without other environmental factors, to truly see the effect. All of these cellular studies, whether they are using model organisms or performing *in vitro*- studies, help research understand the true, immediate consequences of phthalate exposure. Being exposed to phthalates is not like being exposed to an acid, if an individual is exposed to a strong acid- they will most like result in a burn on their skin. When an individual is exposed to phthalates, the effects are not instant, it takes time for the known effects to be observed.

Phthalate concentrations can be found in blood, urine, and sweat (Genuis et al., 2012). The studies mentioned throughout this research include looking at urinary concentration levels, blood work, and even understand the cholesterol serum level. Certain phthalates are found in specific bodily excretions. It should be noted that ‘blood’ and ‘serum’ are synonymous and may be used interchangeably. MEHP and its metabolites can be found in blood, urine, and sweat (Genuis et al., 2012). Whereas DEHP and its metabolites can be found in sweat but not in serum levels, this could be due to phthalate retention and bioaccumulation. Concentrations of phthalates are often studied in the urine of pregnant females (He et al., 2021). Given that phthalates can disrupt the prenatal endocrine system, using the urine of pregnant females can give researchers some idea on whether the not the fetus would suffer from phthalate related illnesses. Whereas animal models had direct exposure to phthalates and were sacrificed to understand the effects, human studies are often based off of surveys on what products individuals may use combined with samples of either urine or blood. Animal models allow researchers to understand direct cause and effects whereas surveying and sampling humans give correlation. Until humans will be allowed to donate their living bodies to science, understanding something like phthalate exposure will take tremendous amounts of time as it needs to be monitored from conception until death and even throughout generations.

The Effects of Phthalate Exposure on Adult Humans

Now that phthalates have been defined and means of exposure have been explained, understanding the true negative effects of phthalates is to truly understand why these molecules are dangerous. As previously mentioned, phthalates are endocrine disruptors and androgens are a major component of the endocrine system. Disrupting androgen production can create a domino effect, beginning from conception all the way to adulthood. Androgens are classified as a group of sex hormones, the most commonly known being testosterone.

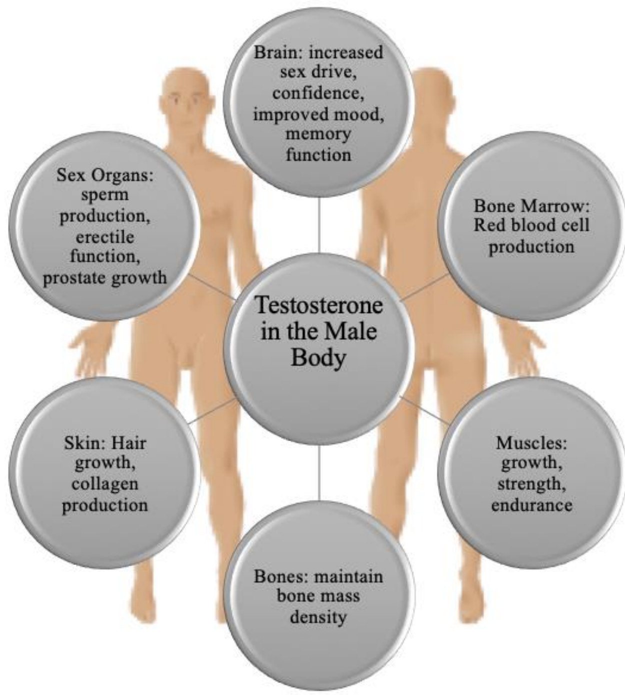


Figure 4: The effects of testosterone within the male body. Image is derived from Miskawaan Health Group (MHG)(n.d.)

Testosterone plays several roles in the body, in both males and females. In men, testosterone is necessary for bone mass, muscle mass, production of red blood cells, as well as fat distribution. Regarding reproductive development, testosterone is crucial for the production of sperm. Testosterone is required for spermatogenesis, a key component of male fertility and without males would otherwise be sterile (Smith & Walker, 2015). Therefore, if male fetuses are exposed to phthalates and potentially suffer androgen deficiency then the negative consequences will ultimately follow them into adulthood. Figure 4 shows the various effects testosterone has on the male body, assuming it is produced properly and is not inhibited. Testosterone, in males, specifically plays a role in red blood cell production, hair growth, bone density, muscle growth, and sperm production along with proper sex organ function. When males are exposed to phthalates, especially prenatally, it can disrupt the pathway that produces testosterone. If a male suffers from improper testosterone production, it can be assumed that all of the things previously mentioned will be stunted as well- resulting in a male that can potentially be sterile (Dobrzynska, 2016).

Along with reproductive challenges, widespread exposure to phthalates is hypothesized to increase blood pressure. Zhagen et al. (2018) created a study aiming to understand the association between blood pressure and serum phthalate concentrations in blood in the Chinese population. 16 different phthalate concentrations were found within serum levels: dimethyl phthalate (DMP), diethyl phthalate, diisobutyl phthalate, dibutyl phthalate (DBP), bis (2-methoxyethyl) phthalate, bis (4-methyl-2-pentyl) phthalate, bis (2-ethoxyethyl) phthalate, diamyl phthalate, dihexyl phthalate, benzyl butyl phthalate, bis (2-nbutoxyethyl) phthalate (DBEP), dicyclohexyl phthalate, bis (2-ethyl hexyl) phthalate (DEHP), diisononyl phthalate, diphenyl phthalate, and di-*n*-octyl phthalate, with DBP being the most dominant contaminant. There was a positive association between concentrations of DMP and DBEP and total cholesterol level in serum (Zhagen et al., 2018). Statistical analysis revealed, in this particular case, that the data gathered wasn't significant however Zhagen et al. (2018) explained that furtherer research is necessary because there was some relationship seen. Healthy serum cholesterol is 200mg/dL and lower. Zhagen et al. (2018) found that DEGP exposure adults had serum cholesterol levels around 296mg/dL, much higher than healthy level. Higher serum cholesterol levels can lead to the potential of fat deposits within blood vessels, these fat deposits have the ability to suddenly break and clot- commonly seen in heart attacks and strokes (Mayo Clinic, 2021). Understanding this in a bigger picture, an individual maybe relatively healthy and actively doing things to combat high blood pressure and high cholesterol- daily exercise and nutrient rich diet, however the presence of phthalates in nearly everyday products can be working against that.

There could be a potential association between phthalate exposure and adiposity in adults, as well (Ribeiro, 2019). Adiposity is excessive energy intake that does not have equivalent expenditure, essentially severe weight gain or obesity (Redinger, 2009). Ribeiro (2019) specifically stated that for MEP there was a positive association found in children and adults, there was no statistical significance. Of the phthalates reviewed, MECP is the only phthalate that showed a significant association with obesity in adults. MECP is a metabolite of DEHP, which, is extensively used in medical devices, building materials, personal care products, and cosmetics despite its well-known toxic and hazardous effects (Rowdhal & Chen, 2018).

The effects of phthalate exposure on female reproduction are not as understood as on male reproduction (Hannon & Flaws, 2015). The lack of understanding is in part due to females are more often exposed to higher levels of phthalates due to cosmetic use and personal care products. Females, on average, use 12 personal care products a day whereas males use 6 products (Environmental Working Group, 2004). Given all the products females use, they have many means of exposure- making it harder to exactly pinpoint which product is causing the greatest amount of phthalate exposure. The ovary is the primary regulator of reproduction within females, specifically being responsible for folliculogenesis and steroidogenesis. Folliculogenesis is the process of maturation of the gametes and steroidogenesis is the synthesis of sex steroid hormones, which are both critical to female production. Exposure to phthalates can induce

[redacted]

Figure 5: The stages of folliculogenesis with the respective genes used for regulation (Alahmad, 2017)

defects in folliculogenesis and steroidogenesis that may result in infertility, non-reproduction, and premature ovarian failure. The direct mechanism at which phthalates can induce negative effects on folliculogenesis is targeting the follicles at different stages (Hannon & Flaws, 2015). Phthalates can target primordial, pre-antral or antral follicles and can even target the corpora lutea. Primordial follicles are the first class of follicles within ovaries and contain an oocyte, remaining dormant until activation. Pre-antral follicles include primordial, primary, and secondary follicles whereas antral follicles include tertiary or ovulatory follicles. Corpora lutea, or corpus luteum, is the hormone-secreting structure that is developed after the ovum is discharged and degenerates unless pregnancy begins. Depending at which stage the follicle is at during phthalate exposure, atresia can occur, follicular arrest, or accelerated development may occur (Hannon & Flaws, 2015). Atresia is defined as the degeneration and resorption of follicles, a version of apoptosis. Looking at the big picture, if phthalate exposure is occurring in females who are at their peak reproduction, successful reproduction may not happen due to the potential effects. Figure 5 shows the various stages of follicular development, similar to male endocrine disruption, a primary or secondary follicle is disrupted due to phthalate exposure then every follicle after is disrupted, creating a downstream effect of consequences. Reiterating the point mentioned, despite how toxic and disrupting phthalates are- their widespread production makes it nearly impossible to ignore. Combining widespread use and environmental contamination, it is suggested that 75% - 100%, of the population of the United States is exposed to phthalates on a daily basis (Wang & Qian, 2021). Of all humans, however, children and fetuses are amongst the highest exposed to phthalates.

The Effects of Phthalate Exposure from the Neonatal period to Infancy

Infants that are in the neonatal intensive care unit that are treated with plastic medical devices, which are made of PVC and contain DEHP, are at risk of being exposed (Boberg, 2018). When infants are intubated, that is a direct oral and inhalation exposure to the plastic, with the phthalates easily migrating from the plastic into the body. This poses a large threat for male infants given that certain phthalates have been understood to interfere with early male reproductive development (Boberg, 2018). Jenkins et al. (2021) explained that common intravenous (IV) products that are used on premature infants have the potential exposure to DEHP. Premature infants that received that received common IV fluids through DEHP positive IV tubing had high concentrations of DEHP metabolites in their urine. DEHP exposure mostly occurred through the use of respiratory devices, specifically the bubble CPAP. Very low weight premature infants that used the bubble CPAP machine had an average DEHP exposure of 182,369 mcg/kg over 80 days of initial hospitalization (Jenkins et al., 2021). The use of the CPAP machine caused greater phthalate exposure than just singular IV use. Data reported that for post-natal exposure to phthalates, there were an increased presences of neurodevelopmental abnormalities, endocrine disruption, genetic anomalies, and hepatic injury (Coster & Larebeke, 2012). Interference this early on is more than likely caused by altering fetal germ cell development of the inhibition of the synthesis of sex steroid hormones. Fetal germ cells are known as the embryonic precursors for mature gametes- sperm or oocytes. Any alterations to the precursors to gametes can be severely detrimental if not fatal and result is drastic error. Potential errors include nondisjunction or polyploidy (Coster & Larebeke, 2012).

Research has also seen an association between phthalates and abnormal reproductive development due to androgen deficiency (Akingbemi & Hardy, 2001; Sharpe, 2001; Zhang et al., 2009). Prenatal exposure to phthalates make fetuses especially susceptible to endocrine disorders (Qian et al., 2020). Prenatal, or before birth, is the time of pregnancy where the fetus is developing within the uterus. The effects of prenatal exposure first disrupt the levels of thyroid, sex hormones, and 25-hydroxyvitamin D. 25-Hydroxyvitamin D is the vitamin D that is absorbed from food. Prenatally, a fetus receives all of its vitamin D from the mother and if phthalate exposure is disrupting these levels, there can be an increased risk of preeclampsia, which has an increased mortality rate. Low vitamin D level is also related to smaller infant size and development of asthma and Type 1 diabetes (Mulligan et al., 2010). Regarding thyroid hormones, within the first trimester of pregnancy, the fetus requires the supply of thyroid hormone from the mother. After the 12^{th} week, the fetuses' thyroid begins to work on its own but doesn't create enough hormone until after the 18^{th} week. If phthalate exposure disrupts thyroid hormones, there is a chance of hypothyroidism- if untreated, the resulting fetus may have a lower than normal IQ and issues with proper development (US Department of Health and Human Services, 2017). Disrupting sex hormone levels can result in improper sexual differentiation of the fetus. If phthalate exposure disrupts any of the aforementioned levels, the likelihood of preterm birth, preeclampsia, maternal glucose disorders, infant cryptorchidism, infant hypospadias and shorter anogenital distance (Qian et al., 2020). Infant cryptorchidism is a condition where either one or both of an infant male's testicles have not properly descended into the scrotum. Untreated cryptorchidism can lead to testicular torsion or loss of testicle as well as potentially cause sterility. Infant hypospadias is a birth defect where the opening of the urethra is not located properly at the tip of the penis. If hypospadias is not corrected, difficulties in sexual function, voiding, and psychosexual adjustment may occur. Anogenital distance is the distance between the anus to the genitals and is seen as a marker to androgen exposure. Shorter than normal anogenital distance can be associated with infertility, testicular function, and even increased feminization (Pedersen, Osther & Rafaelsen, 2021). Figure 6 shows the different places where phthalate exposure may come from and the respective effects on pregnant woman and offspring. Even if the fetus is born without immediate noticeable anomalies, there is the potential that it could have stunted fetal growth or even high blood pressure- symptoms that are only seen after time has passed.

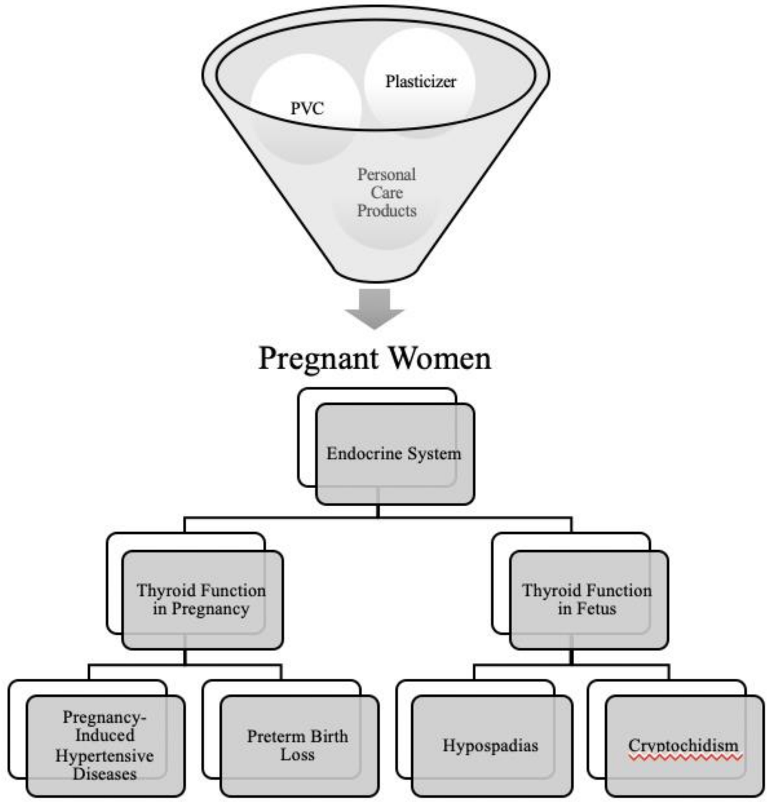


Figure 6: The sources of phthalate exposure for pregnant woman and the effects on the endocrine in both the mother and the fetus. Image derived from (Qian et al., 2020)

Models of phthalate exposure mentioned a potential relationship between phthalate exposure and asthma. Dibutyl phthalate is seen to cause dysregulation of thymic stromal lymophopoietin expression- a gene that is linked to asthma and allergen disease (Wang et al., 2021). Specifically, dibutyl phthalate causes the upregulation of the TSLP gene, combining this with the potential of DNA methylation that occurs due to environmental exposure of phthalate may result in asthma and increased allergic reaction. Overall, Wang et al. (2021) determined that benzyl butyl phthalate, BBzP, is positively associated with children's respiratory symptoms by decreasing TSLP methylation. Therefore, children who have allergen diseases should aim to reduce the potential exposure of BBzP. Further research revealed that even prenatal exposure to BBZP can be linked with eczema (Just et al., 2012). The concentration of BBzP, which is the main metabolite in urine, was measured during the third trimester- being detected in over 99% of samples. Of the mothers that had BBzP detected, by 24 months nearly 30% of infants were noted to develop eczema, and even up to 48% for African Americans. The statistical analysis did reveal that BBzP was not associated with eczema however prenatal exposure to BBzP may influence the potential of developing eczema during childhood.

Prenatal phthalate exposure may also be associated with autism spectrum disorder. In a study performed by Shin et al. (2018), 14 metabolites of 8 phthalates were collected from urine samples that were obtained during the second and third trimester of pregnancy. 201 mothers provided urine samples, with 46 of them giving birth to children with autism spectrum disorder, 55 giving birth to non-typical development and 100 giving birth for typical development. Male children had MEP, monobenzyl phthalate, and other metabolites with positive association with non-typical development. It has been noted that children between the ages of eight to eleven were seen to have an association between metabolites of DEHP and attention deficit hyperactivity disorder (Kim et al., 2009). Despite the fact there is no statistical significance between autism spectrum disorder and phthalate exposure, the sheer number of findings play into the biological plausibility of effects happening. The biological plausibility is considerable given all means of exposure, whether it is due to direct effect using personal care products or indirect due to the presence of phthalates in the environment. Prenatal exposure can also occur without the mother's direct effect. Studies have also found that presence PVC flooring during pregnancy and the first year of child development were related to an increased risk of autism spectrum disorder, more specifically higher concentrations of DEP and DBP were related to higher presence of inattention and hyperactivity-impulsivity that is seen within children who have autism spectrum disorder (Philippat et al., 2015). It is important to understand that even an individual who has not been born yet can suffer from phthalate exposure and may be potentially at risk for negative side effects.

Conclusion

A point that has been reiterated several times throughout this analysis is that phthalate exposure leads to a multitude of negative effects. Whether it occurs prenatally or it is continuous exposure throughout adulthood, there is risk with any form. Something to understand is that if any individual makes lifestyle decisions to eliminate as many products as they can that contain phthalates, it doesn't eliminate them from the environment and presence of metabolites in the air. With every item that goes into a landfill that is full of phthalates, those phthalates seep into water and air and are continuously breathed in and ingested. As previously mentioned, phthalates are often used in medical supplies- specifically tubing and gloves. A general surgeon or really any hospital staffer is at increased exposure risk than someone who works a different career path. While the consequences of phthalate exposure are highly known, the use of phthalates in medical equipment is necessary due to the strain medical equipment goes through. It is necessary to create gloves that do not easily tear in surgical settings to prevent contamination and create tubing that can withstand constant liquid flow. Until this is a better alternative to phthalates, the use of them as durable plasticizers will continue to grow. It is important to note that the majority of research cited in this analysis is no more than 15 years old, most being under 10 years old, meaning that the research for the effects of phthalate exposure is relatively new and still being understood. Despite how young the research is, the negative consequences that have been described to be associated with phthalate exposure are drastic- beginning from conception all the way into old age. Phthalate exposure is everywhere, whether it be in the personal care product someone curates for themselves, or just seeping into the air from landfills, exposure is inevitable but given all the negative side effects of it- there must be something done to prevent future increased exposure.

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