Effects on Female Reproductive Systems Caused by the Use of Phthalate-Containing Medical Devices

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Introduction

By definition, a phthalate or a phthalate ester is a large group of man-made, synthetic chemicals with a large and varying industrial use (Lovekamp-Swan, Davis, 2003). Phthalates are a commonly used plasticizer, that are found in thousands of products including detergents, perfumes, hair spray, shampoos, soap, vinyl flooring, pipes, cable coatings, sealants, automotive parts, and containers (Hannon, Niermann, Flaws, 2016).This means that there are several different types of phthalates, which can complicate exposure and toxicity assessments. However, in this paper, the phthalate-containing product that will be highlighted here are medical devices.

It is important to first note that while most researchers say that phthalates do not bioaccumulate in the body, and that they get entirely metabolized and excreted out, a recent study by Genuis, et al., in 2012 published their article speculating that statement (Genuis, Beesoon, Lobo, Birkholz, 2012). In their study, 20 individuals had their blood, urine, and sweat collected and tested for phthalate compounds and metabolites (Genuis, et al., 2012). According to their results, MEHP concentrations were two times the amount in sweat than in urine (Genuis, et al., 2012). However, in individuals where DEHP was found, several people had DEHP found in their sweat, but not in their serum (Genuis, et al., 2012). Researchers found that suspicious, and think that there may be bioaccumulation occurring within the human body, and could be contributing to the toxicity of DEHP (Genuis, et al., 2012). In spite of this recent data, it is hard to exactly say whether (Genuis, et al., 2012) bioaccumulation of phthalates is occurring in the human body, and would therefore require much more research, so researchers could get a clearer understanding of phthalates and their effects.

Medical devices contain polyvinyl chloride, a hard material in plastic products, and a plasticizer such as a phthalate like di-(2-ethylhexyl) phthalate (DEHP) or di-*n*-butyl phthalate (DBP) that increases the flexibility and durability of the medical devices (Center for Devices and Radiological Health, USFDA, 2003). With over 18 billion pounds of phthalates being used every year, and 500 million pairs of disposable medical equipment and sterile gloves being produced, DEHP is one of the most commonly used phthalate in medical devices (Lovekamp-Swan, Davis, 2003). Some commonly used phthalate-containing medical devices that patients are exposed to most include, IV bags, blood bags, blood and respiratory tubing, feeding tubes, catheters, and dialysis tubing (Center for Devices and Radiological Health, USFDA, 2003). These phthalates in medical devices display endocrine disrupting characteristics such as estrogenic properties that can have potentially harmful effects on fetal development and the female reproductive system (Lovekamp-Swan, Davis, 2003). Some potential effects of phthalate exposure include fetal resorption or death, fetal malformations, decreased estradiol levels and number of follicles, and altered estrous cycles (Lovekamp-Swan, Davis, 2003)(Hannon, et al., 2016) (Shiota, Nishimura, 1982). As a society, not only should we be more consciously aware of what we are putting in or on our bodies, but also what things are made of. The effects from exposure to phthalates can have the potential to be detrimental to the health of yourself and your future children.

Daily Levels of Exposure to Phthalates

Without even knowing, women subject themselves to higher levels of exposure through the daily use of multiple personal care products, such as scented lotions, perfumes, shampoo, soaps, detergents, and hair spray (Parlett, Calafat, Swan, 2013).

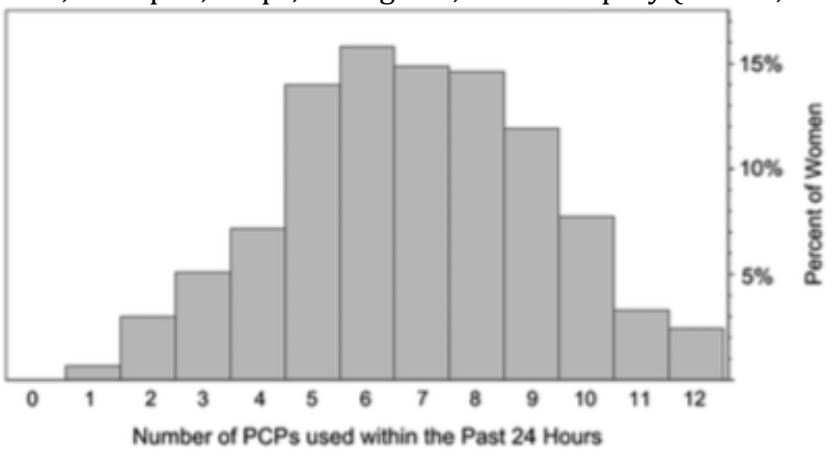

Figure 1: Shows the number of Personal Care Products each woman used within the past 24-hour period (Parlett, et al., 2013).

According to Figure 1, approximately 50% of women are exposing themselves to 5-8 personal care products that potentially contain phthalates (Parlett, et al., 2013). It is important to point out that this is only within the past 24-hour period, and includes no other exposure to phthalates other than personal care products. This means that in addition to exposure to these potentially phthalate-containing personal care products, women are also potentially exposing themselves to other phthalates through different routes of exposure (Parlett, et al., 2013).

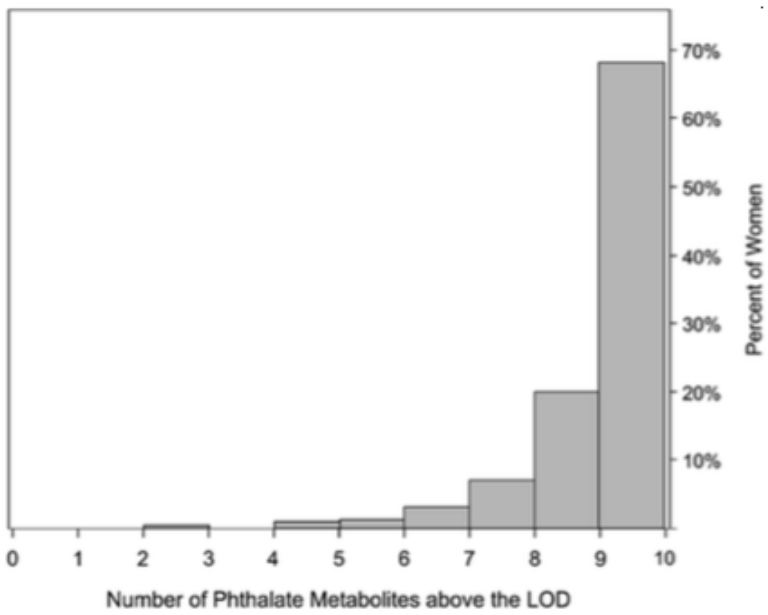

Figure 2: Shows the percent of women and the number of phthalate metabolites in their urine above the level of detection (Parlett, et al., 2013).

Figure 2 gathers the number of women above the limit of detection (LOD), 24-hours after reporting their exposure to personal care products (Parlett, et al., 2013). The LOD is the lowest quantity or amount that a substance can be detected as, thus different substances will have different levels of detection (Parlett, et al., 2013). However, in this experiment, all of the phthalate metabolites tested for were within a factor of 0.66-0.72 (Parlett, et al., 2013). Therefore explaining that not only must their be phthalates in their personal care products, but also the amount of phthalates still left in their system after 24-hours, and the number of phthalate metabolites in their systems are above the (LOD) limit of detection (Parlett, et al., 2013).

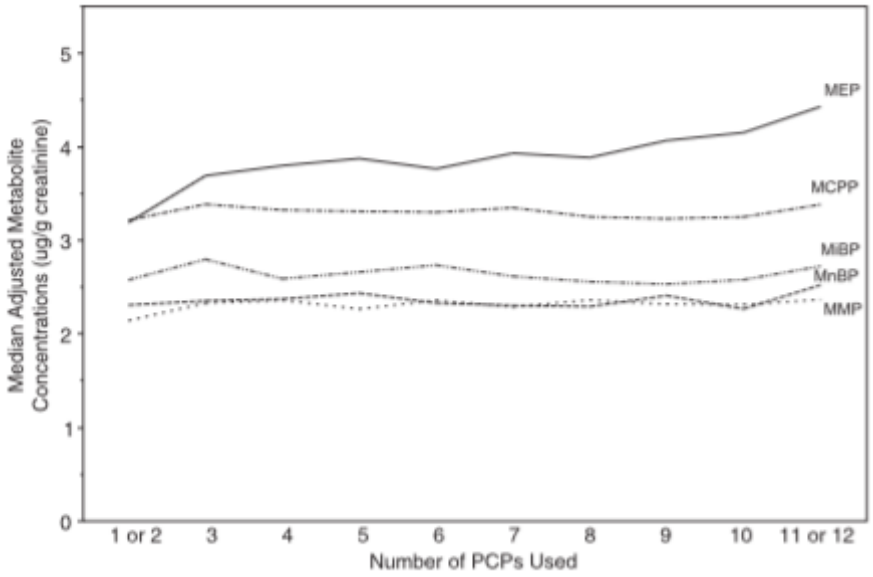

Figure 3: Shows the median level of phthalate metabolites in comparison to the number of personal care products that were used within the past 24 hours (Parlett, et al., 2013).

Figure 3 essentially demonstrates that as the number of personal care products containing phthalates increases, the level of phthalate metabolites found in the women's urine, also increases (Parlett, et al., 2013). This also coincides that with higher levels of exposure to phthalates, there is a higher potential risk of the damaging effects of phthalates (Parlett, et al., 2013). The overall data suggests that the products and the number of phthalate-products being used are related to the concentration of phthalate metabolites in the women's urine (Parlett, et al., 2013). By reducing the use or number of phthalate-containing personal care products, not only could one reduce their costs of living, but could also reduce their overall daily and lifelong phthalate exposure (Parlett, et al., 2013).

Levels of Exposure to Phthalates through Medical Devices

The general population is exposed to approximately 2 mg of phthalates each day through sources like water bottles, plastic containers, and personal care products. This equates to about 0.0263 mg/kg each day for an average female weighing about 168 pounds (Lovekamp-Swan, Davis, 2003) (National Center for Health Statistics, n.d.). Through occupational and medical exposures, there is an even larger increase

in the level of phthalates we are being exposed to (Center for Devices and Radiological Health, USFDA, 2003). Our own FDA has published a safety assessment of DEHP in PVC medical devices (Center for Devices and Radiological Health, USFDA, 2003). The use of these medical devices during specific medical procedures, highly expose us to high levels of phthalates, and in particular, DEHP (Center for Devices and Radiological Health, USFDA, 2003)

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Table 1: Shows a table of estimated, or expected levels of exposure doses of DEHP while undergoing different medical procedures, using different medical equipment for both adults and neonates (Center for Devices and Radiological Health, USFDA, 2003).

Procedure	DEHP dose (mg/kg/day)	
	Adult (70 kg)	Neonate (4 kg)
Infusion of crystalloid IV solutions	0.005	0.03
IV infusion of drugs requiring pharmaceutical vehicles for solubilization		
When administered according to manufacturer's instructions	0.04	0.03
When stored mixed and stored at room temperature for 24 hr	0.15	
TPN administration		
Without added lipid	0.03	0.03
With added lipid	0.13	2.5
Administered via EVA bag and PVC tubing	0.06	
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO in adult patient	3.0	
Exchange transfusion/neonate		22.6
Replacement transfusion/neonate in NICU		0.3
Replacement transfusion/correction of anemia in patients receiving chemotherapy and in patients with sickle cell disease	0.09	
Replacement transfusion/surgical patient undergoing CABG	0.28	
Treatment of clotting disorders with cryoprecipitate	0.03	
Cardiopulmonary bypass		
CABG	1	
Orthotopic heart transplant	0.3	
Artificial heart transplant	2.4	
ECMO		14
Apheresis	0.03	
Hemodialysis	0.36	
Peritoneal dialysis	< 0.01	
Enteral nutrition	0.14	0.14

Table 1 shows the estimated phthalate dose one would be exposed to if they were to undergo that medical procedure at this moment, for both adults and neonates (Center for Devices and Radiological Health, USFDA, 2003). For example, if an individual went to the emergency room with symptoms of dehydration, the

nurse or doctor would use a saline IV. If the patient was an adult weighing approximately 70 kg, or 154 lbs., they would be exposed to 0.005 mg/kg/day of DEHP, on top of their daily exposure of 0.0285 mg/kg/day (Center for Devices and Radiological Health, USFDA, 2003). However, if the patient was a neonate weighing 4 kg, or 8.8 lbs., they would be exposed to 0.03 mg/kg/day (Center for Devices and Radiological Health, USFDA, 2003). The neonate would be exposed to more DEHP than the average adult weighing 70 kg by something as simple as an IV (Center for Devices and Radiological Health, USFDA, 2003). Also, some of these medical devices are used in conjunction with one another, ultimately exposing adults and neonates to an even higher level of phthalates (Center for Devices and Radiological Health, USFDA, 2003). What will be proven later on in this paper, is that at higher doses of these phthalates, especially DEHP, there is an even higher risk of these effects potentially occurring when we are exposed to these types of levels of phthalates (Lovekamp-Swan, Davis, 2003) (Hannon, et al., 2016) (Shiota, Nishimura, 1982). As a patient, and as a woman, one should be particularly concerned about being exposed to these high levels of phthalates on top of their normal, daily levels of exposure. As levels of phthalate exposure continue to increase, whether it be through daily exposure or through medical devices, effects will become more and more prevalent (Lovekamp-Swan, Davis, 2003) (Hannon, et al., 2016).

Effects of Phthalate Exposure on Fetal Mice

There is cause for concern with phthalate exposure for women specifically, and therefore raises more potential health problems, especially for a female's reproductive system and the health of their future children. As many know, a woman's reproductive system is vital for the growth and development of a fetus, and when exposed to phthalates during pregnancy, several developmental toxicological effects related to the health of the fetus occur (Shiota, Nishimura, 1982). Some of these effects include reduced implantations, fetal malformations, a decrease in the body weight of the fetus, and even the loss of the fetus (Shiota, Nishimura, 1982).

In a study done by Shiota and Nishimura, pregnant female mice were exposed to DEHP and DBP through diet during fetal development at varying doses (Shiota, Nishimura, 1982). In order to truly understand the effects and the severity of the problem, the actual dosages of the phthalates need to be converted in the table, as well as calculated into the human equivalency of the average female weight in the United States. (National Center for Health Statistics, n.d.). The phthalate dose percentage of DEHP is 1.0%, 04%, 0.2%, 0.1%, and 0.05%, equal to 2200 mg/kg/day, 830 mg/kg/day, 410 mg/kg/day, 190 mg/kg/day, and 70 mg/kg/day, respectively (Shiota, Nishimura, 1982). The average weight of a mouse equals 0.0193 kg, and the average weight of a female in the United States is 76.4 kg (National Center for Health Statistics, n.d.). When these dosages are equated to a the average weight of a human female, the doses are as followed, 0.556 mg/kg/day, 0.209 mg/kg/day, 0.103 mg/kg/day, 0.0482 mg/kg/day, 0.0177 mg/kg/day, respectively (Shiota, Nishimura, 1982). The phthalate dose percentage of DBP is 1.0%, 04%, 0.2%, 0.1%, and 0.05%, and equal 2100 mg/kg/day, 660 mg/kg/day,

370 mg/kg/day, 180 mg/kg/day, and 80 mg/kg/day, respectively (National Center for Health Statistics, n.d.). When these dosages are equated to the average weight of a human female, the doses are equated to, 0.539 mg/kg/day, 0.167 mg/kg/day, 0.0934 mg/kg/day, 0.0454 mg/kg/day, and 0.0202 mg/kg/day, respectively (Shiota, Nishimura, 1982). It is important to note the human equivalencies of these doses because not only are they close to the average daily exposure to phthalates, of 0.0262 mg/kg/day, but they are similar levels of exposure when in comparison to mice where fetal deaths and malformations were being seen in the results of the two tables below (Lovekamp-Swan, Davis, 2003) (Shiota, Nishimura, 1982). It will be important to reference these human equivalences throughout the rest of this study.

Some of the initial effects analyzed of DEHP and DBP showed the number of deaths of the fetuses in comparison to the number of implants done, as well as the corresponding phthalate and phthalate dosage, see Table 2 (Shiota, Nishimura, 1982).

Table 2: Shows the phthalate dose that the pregnant mice were exposed to in relation to the number of litters, the number of successful implants, and the number of fetal deaths (Shiota, Nishimura, 1982).

Phthalate	Phthalate dose, %	Number of litters	Number of implants (means ± SE)	Resorptions and dead fetuses, %	Fetal weight, g (mean ± SE)	
					Male	Female
DEHP	1.0	12	12.6 ± 0.5	100.0[a]	–	–
DEHP	0.4	7	15.0 ± 1.2	100.0[a]	–	–
DEHP	0.2	24	11.1 ± 0.9	67.8[a]	1.12 ± 0.07[a]	1.16 ± 0.04[b]
DEHP	0.1	9	12.6 ± 2.1	31.0[c]	1.28 ± 0.08	1.21 ± 0.07
DEHP	0.05	8	13.3 ± 1.7	7.5	1.32 ± 0.07	1.29 ± 0.06
DBP	1.0	15	12.1 ± 0.5	98.4[a]	1.03, 1.24	0.80
DBP	0.4	9	12.0 ± 0.8	11.4	1.10 ± 0.18[b]	1.06 ± 0.20
DBP	0.2	21	12.4 ± 0.8	22.3	1.31 ± 0.07	1.24 ± 0.06
DBP	0.1	8	12.0 ± 2.9	11.2	1.29 ± 0.10	1.22 ± 0.08
DBP	0.05	7	12.7 ± 3.1	3.7	1.31 ± 0.04	1.29 ± 0.03
Control	—	8	10.8 ± 1.9	5.0	1.41 ± 0.07	1.35 ± 0.07

[a]Significantly different from control mice ($p < 0.01$).
[b]Significantly different from control mice ($0.01 < p < 0.05$).
[c]Difference from controls is at the borderline level of significance ($p \approx 0.05$).

Table 2 displays the high resorption rate, or fetal deaths at high levels of DEHP and DBP, thus exhibiting a dose dependent relationship (Shiota, Nishimura, 1982). From the dose-dependent relationship, we can conclude that at high levels of exposure to phthalates, specifically DEHP and DBP, there are effects on a female's reproductive system, ultimately causing the mother to lose the fetus at some point during pregnancy (Shiota, Nishimura, 1982). As explained earlier, exposure to these phthalates can also cause additional effects. In table 3, there were a large number of fetal malformations at lower doses of phthalates exposure (Shiota, Nishimura, 1982). This again reinforces the dose-dependent response.

Table 3: Shows the specific fetal malformations, as well as the number of each malformation at the lower dosages of phthalates (Shiota, Nishimura, 1982).

Phthalate	Phthalate dose, %	Number (%) of malformed fetuses	Type of malformation and (no. of cases)[c]
DEHP	1.0	—	—
DEHP	0.4	—	—
DEHP	0.2	14 (25.8)[a]	Ex (3), Ex + OE (2), Ex + TA (1), My (1), My + GS + CF (1), My + OE + GE (1), GS + TA (1), TA (4)
DEHP	0.1	3 (5.3)	Ex (2), OE (1)
DEHP	0.05	0 (0.0)	—
DBP	1.0	2 (75.0)[b]	Ex (2)
DBP	0.4	0 (0.0)	—
DBP	0.2	1 (0.5)	OE (1)
DBP	0.1	0 (0.0)	—
DBP	0.05	0 (0.0)	—
Control	—	0 (0.0)	—

[a]Significantly different from control mice ($p < 0.05$).
[b]Difference from controls is at the borderline level of significance ($p \approx 0.05$).
[c]Type of malformation: CF club foots; Ex, exencephaly; GE, generalized edema; GS, gastroschisis; My, myeloschisis; OE, open eyelids; TA, tail anomaly.

Table 3, as previously mentioned, shows the number of malformed fetuses at specific phthalate dosages, as well as the type of malformations that are being seen (Shiota, Nishimura, 1982). Some of the malformations being seen include club foot, exencephaly, which is a cephalic disorder where the brain of a fetus is located outside of the skull, and gastroschisis, which is another birth defect where the intestines of the baby are found outside of the abdominal wall (Shiota, Nishimura, 1982). Other malformations found in the mice during this experiment were generalized edema, myeloscisis, open eyelids, and a tail anomaly (Shiota, Nishimura, 1982).

Not only did DEHP and DBP cause malformations in mouse fetuses as previously mentioned above, but also caused effects to the skeletal development of mice too (Shiota, Nishimura, 1982).

Table 4: This table shows the effects of the phthalates DEHP and DBP on the skeletal development of the fetuses (Shiota, Nishimura, 1982).

Phthalate	Phthalate dose, %	Number of fetuses examined	Skeletal malformations	Variations (%)		Number of ossified coccygia (mean ± SE)
				Lumbar rib	Deficient ossification of sternebrae	
DEHP	1.0	0	–	–	–	–
DEHP	0.4	0	–	–	–	–
DEHP	0.2	40	0	18.7	8.3	6.5 ± 0.6[a]
DEHP	0.1	35	0	20.7	14.7	9.2 ± 0.3
DEHP	0.05	31	0	7.6	0.0	7.3 ± 0.4[a]
DBP	1.0	0	0	–	–	–
DBP	0.4	42	0	36.9	0.0	2.6 ± 0.4[a]
DBP	0.2	65	0	26.3	0.0	6.0 ± 0.4[a]
DBP	0.1	38	0	17.2	0.0	4.5 ± 0.3[a]
DBP	0.05	41	0	23.8	6.3	5.1 ± 0.3[a]
Control	—	0	0	13.3	0.0	9.4 ± 0.2

[a]Significantly different from control mice ($p < 0.05$).

According to Table 4, at a median to lower phthalate dosage, there were skeletal anomalies present (Shiota, Nishimura, 1982). Despite there not being a statistical significance in the lumbar rib and deficient ossification of sternebrae column, there was still a difference between the control and treatment groups that

showed the presence of extra lumbar ribs and the increased levels of deficient ossification of the sternebrae (Shiota, Nishimura, 1982). However, there was a statistical significance in delayed ossification of the coccygeal in all fetuses, except for the DEHP 0.1%, 190 mg/kg/day, treatment group (Shiota, Nishimura, 1982).

While these results shows some drastic and life-threatening fetal effects, and in fact DEHP and DBP can have the potential of affect fetal development, it is important to note that the doses administered to the mice were almost 2000 times the estimated human exposure back in 1982 (Shiota, Nishimura, 1982). That being said, a more current human exposure estimate from 2003 was close to 2 mg/day, which equates to a human female equivalency of 0.0262 mg/kg/day (Lovekamp-Swan, Davis, 2003) (Shiota, Nishimura, 1982). The daily exposure level estimated from 2003, is not far away from some of the phthalate doses that were causing malformations or even fetal deaths in the mice (Lovekamp-Swan, Davis, 2003) (Shiota, Nishimura, 1982). As this article just became more relevant to the exposure rates of phthalates in humans, it is important that more research be done, so a clearer picture of the effects of phthalates in humans can be seen.

Effects of Phthalates on the Female Reproductive System: Estradiol Levels

The effects of phthalates on fetal exposure and the female reproductive system have been heavily researched, however the mechanisms that cause these effects still require much more exploration. In a review paper by Lovekamp-Swan and Davis, they analyzed the data originally collected by Davis, BJ, et al., on *Di-(2-ethylhexyl) phthalate suppresses estradiol production and ovulation in cycling rats,* and found that DEHP decreased the estradiol production, and proposed a mechanism that explained that the ovary was the target for DEHP, ultimately explaining why estradiol levels decreased in mice (Lovekamp-Swan, Davis, 2003).

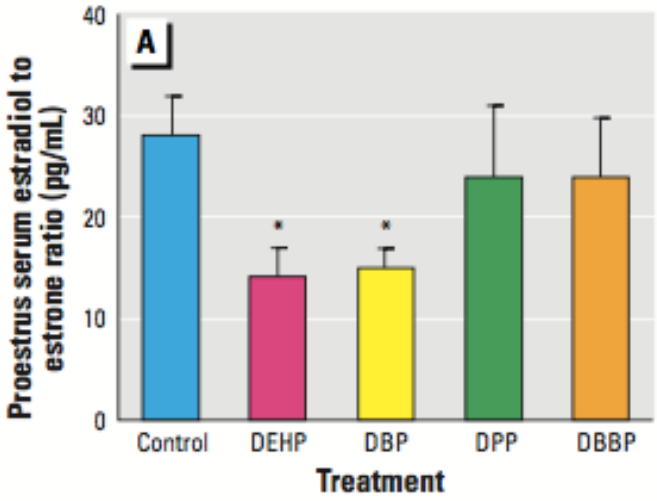

Figure 4: Shows the effects of phthalates on estradiol and estrone levels at the proestrus stage of ovulation (Lovekamp-Swan, Davis, 2003).

In the original study, the mice were treated with 1000 mg/kg/day for 12 days of DEHP, DBP, and other phthalates. In order to make these doses relevant to

human exposure, values were again calculated to the human equivalency of an average woman's weight in the United States, which was calculated out to be 0.263 mg/kg/day (Lovekamp-Swan, Davis, 2003) (National Center for Health Statistics, n.d.). From figure 4, part A, the results display that when mice were treated specifically with the phthalates DEHP and DBP, estradiol levels significantly decreased during the first stage of the reproductive cycle, called proestrus (Lovekamp-Swan, Davis, 2003). When estradiol levels reach a certain level it causes a subsequent surge of Luteinizing Hormone (LH), which then triggers ovulation, thus with the decrease in estradiol production, ovulation will not be triggered (Lovekamp-Swan, Davis, 2003). In order to conclude if the ovaries and estradiol levels were the primary target of toxicity, a compound similar to LH was used to stimulate ovulation (Lovekamp-Swan, Davis, 2003). Because ovulation did occur in these mice when stimulated, the researchers were able to confirm that it was the ovaries that were the primary location of toxicity when exposed to DEHP and DBP (Lovekamp-Swan, Davis, 2003). Consequences of the decrease in estradiol levels include longer estrous cycles and lack of ovulation, and if there is no ovulation occurring, there will be no corpora luteal, and follicles will then become cystic (Lovekamp-Swan, Davis, 2003). This means that because the ovary is the origin of these follicles that produces the estradiol, there is consequently a decrease in the production of estradiol, therefore explaining that DEHP and DBP specifically targets the ovaries (Lovekamp-Swan, Davis, 2003).

Proposed Mechanism of Phthalates on Estradiol Levels

In the review paper by Lovekamp-Swan, et al., the researchers proposed a potential mechanism in which the phthalates such as DEHP, target the ovaries and alter estradiol levels (Lovekamp-Swan, Davis, 2003). First, DEHP acts on the membrane to inhibit Follicle-stimulating Hormone (FSH) from binding (Lovekamp-Swan, Davis, 2003). This activates an inhibitory Gi protein, and because FSH would otherwise stimulate cAMP production, the inhibition of FSH from binding decreases cAMP production (Lovekamp-Swan, Davis, 2003). Then DEHP diffuses across the membrane and activates Peroxisome Proliferator-Activated Receptors (PPARs), specifically PPARα and PPARγ (Lovekamp-Swan, Davis, 2003). By activating PPARα and PPARγ, it subsequently decreases aromatase transcription of granulosa cells, a somatic cell of the female reproductive system (Lovekamp-Swan, Davis, 2003). Due to the fact that aromatase converts androgens from the thecal cells into estradiol, it thereby decreases the production of estradiol (Lovekamp-Swan, Davis, 2003). In addition, when the PPARα and PPARγ are activated, it increases the mRNA for fatty acid binding proteins (FABP) in the granulosa cells to which PPARs can bind (Lovekamp-Swan, Davis, 2003). By increasing the number of binding proteins for PPAR activators, that decrease aromatase transcription, it results in the decrease of estradiol production (Lovekamp-Swan, Davis, 2003).

Effects of Phthalates on the Female Reproductive System: Estrus Cycle

As discussed in the proposed mechanism that DEHP targets the ovaries and essentially disrupts processes necessary for reproductive health, this study

highlighted the adverse effects on female reproductive systems in adulthood, through the acute exposure of DEHP in mice (Lovekamp-Swan, Davis, 2003) (Hannon, et al., 2016). In summary, adult female mice were exposed to an oral dose of DEHP, at varying dosages, for 10 days, and their reproductive systems were evaluated against their controls at six and nine months past their dosing date (Hannon, et al., 2016). Dosages of DEHP used were 20μg/kg/day, 200 μg/kg/day, 200 mg/kg/day, 200 mg/kg/day, and 500 mg/kg/day. When converted to a human female's equivalency, doses were 0.00507 μg/kg/day, 0.0507 μg/kg/day, 0.00507 mg/kg/day, 0.0507 mg/kg/day, and 0.127 mg/kg/day, respectively. They found that DEHP significantly influenced the estrous cycle at both the six and nine-month mark by altering the length in the number of days in which the mice were in the stages of estrus, metestrus/diestrus (Hannon, et al., 2016). The estrous cycle is linked to a much larger problem, fertility (Hannon, et al., 2016). Any disruption or alteration in the estrous cycle can result in a problem with fertility, as well as be an indicative of a disruption in steroidogeneisis and the Hypothalamic-Pituitary-Ovarian axis, ultimately the hormonal control of the menstrual cycle (Hannon, et al., 2016).

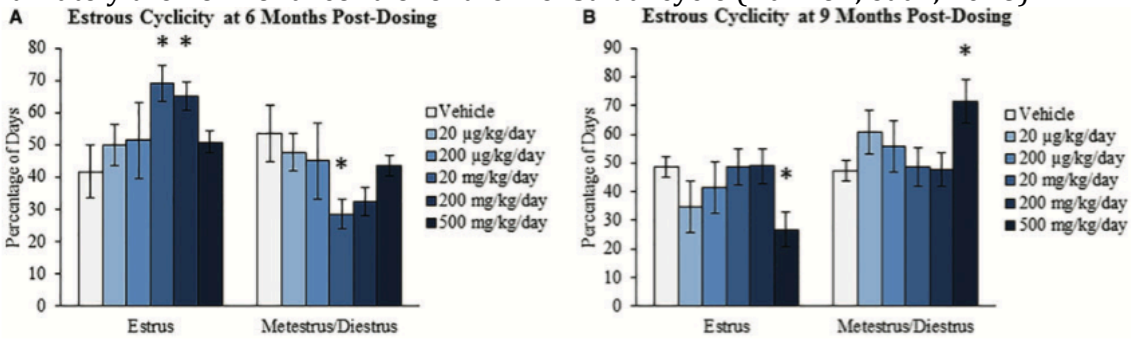

Figure 5: Shows both the 6-month mark and the 9-month mark of each Estrous Cycle. Within each Estrous Cycle, it also breaks down the percentage of days that the mice spent within the estrus and metestrus/diestrus stages (Hannon, et al., 2016).

Figure 5 ultimately showed that there is definitely a change in the estrous cycle between the control and treatment groups of mice (Hannon, et al., 2016). Results showed that at the 6-month mark in the estrus part of the cycle, that the mice dosed with 20 mg/kg/day and 200 mg/kg/day had an increase in the percentage of days that the mice were in the estrus stage of the cycle (Hannon, et al., 2016). Also in the 6-month mark, in the mestestrus/diestrus stage of the estrus cycle, the mice dosed with 20 mg/kg/day showed a decrease in the percentage of days that the mice were in that stage (Hannon, et al., 2016). In Part B in Figure 5 that displayed the 9-month mark post-dosing, results were slightly different (Hannon, et al., 2016). In both of the estrus and the mestestrus/diestrus stage of the cycle, the only dosage that showed results was the mice dosed with 500 mg/kg/day; showing a decrease in the percentage of days in the estrus stage, but an increase in the percentage of days in the mestestrus/diestrus stage (Hannon, et al., 2016). These results ultimately give rise to the conclusion that these phthalates do have long-term permanent effects of the reproductive health of females, but specifically at higher doses, and continue to have effects on the estrous cycle, even later on in life (Hannon, et al., 2016).

Amongst these effects, they also discovered effects on ovarian-derived hormones, but only during the 9-month mark past the dosing (Hannon, et al., 2016). One specific hormone, Inhibin B, at dosage levels of 200 mg/kg/day and 500 mg/kg/day, felt the effects of phthalate exposure, by ultimately decreasing the levels of their secretion (Hannon, et al., 2016). Inhibin B, when secreted, reflects the number of follicles in the ovary, and when levels of Inhibin B are decreased, so are the number of follicles, ultimately accelerating earlier reproductive aging (Hannon, et al., 2016).

Effects of Phthalates on the Female Reproductive System: Folliculogenesis

In the same study done by Hannon, et al., 9 months after the mice had been exposed to DEHP, at varying doses, as listed above, one ovary was taken from each mouse, and each follicle within the ovary was examined to determine which stage of follicular development, either primordial, primary, preantral, or antral, the follicle had attained (Hannon, et al., 2016). Results were then analyzed and put into categories according to dosage or stage of the follicular development (Hannon, et al., 2016).

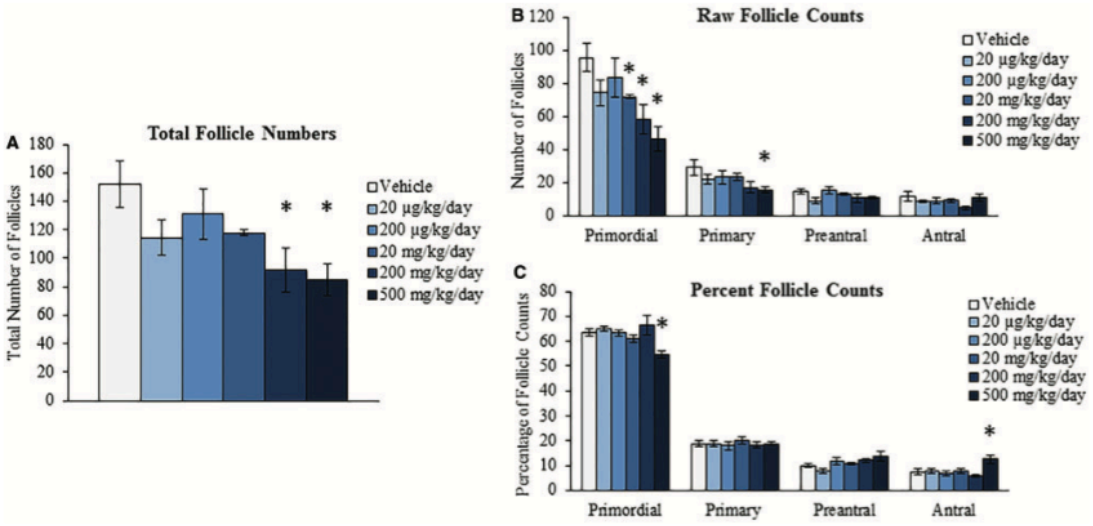

Figure 6: Shows the effect of DEHP 9-months after dosing (A)on the total number of follicles, (B) the number of follicles for primordial, primary, preantral, and antral follicles, and (C) the percentage of follicles left for primordial, primary, preantral, and antral follicles (Hannon, et al., 2016).

In figure 6, part a, it displays a statistically significant decrease in the total number of follicles in the mice dosed with 200 mg/kg/day and 500 mg/kg/day of DEHP (Hannon, et al., 2016). In part B, there is also a statistically significant decrease in the number of primordial follicles in the mice dosed with 20 mg/kg/day, 200 mg/kg/day, and 500 mg/kg/day of DEHP (Hannon, et al., 2016). Also in part B, there was a significant decrease in the number of primary follicles in the mice dosed with 500/mg/kg/day of DEHP (Hannon, et al., 2016). In part C of the same figure, the number of follicles was converted into a percentage to show the percentage of the number of follicles left in each stage (Hannon, et al., 2016). The only statistically significant data was for the 500 mg/kg/day of the primordial follicles and the antral follicles (Hannon, et al., 2016). As previously mentioned, this data displays a dose

dependent relationship; at higher levels of exposure to DEHP, the more effects are seen.

Disruption of folliculogenesis, the maturation of an ovarian follicle, occurs by decreasing the number of primordial follicles and increasing the number of primary follicles, and is another detrimental effect caused by exposure of DEHP (Hannon, et al., 2016). At birth there is a set number of primordial follicles, and is ultimately a female's reproductive lifespan (Hannon, et al., 2016). Typically, at as one gets older, and a female transitions into menopause, the decrease in the number of primordial follicles because they are nonrenewable, or not able to regenerate, is indicative of reproductive aging, also called menopause (Hannon, et al., 2016). However, when there is a disruption in maturation of an ovarian follicle that occurs, it can potentially cause infertility as well as premature ovarian failure, and advance reproductive aging (Hannon, et al., 2016). Results showed a significant decrease in the number of follicles counted in the mice exposed to 200 mg/kg/day and 500 mg/kg/day at the 9-month mark past their dosing in comparison to the control group (Hannon, et al., 2016). Therefore, these particular mice have the potential to experience infertility, early reproductive aging, and premature ovarian failure (Hannon, et al., 2016).

Conclusion

All effects considered, there are certain measures that can be taken to reduce your levels of phthalate exposure, especially for pregnant women or women planning to get pregnant. A seemingly simple method to reduce your phthalate exposure is by reducing the number of personal care products, or by replacing them with phthalate-free personal care products. Also, avoid using plastic containers, and especially avoid microwaving plastic containers. Glass containers are an effective solution, and are typically safe to microwave. Other products that contain phthalates are soaps, detergents, deodorant, body wash, perfume, and essentially anything with a fragrance (Parlett, et al., 2013). While I understand it is hard to eliminate all phthalates from your daily lives, there are alternatives, such as fragrance-free options, or just overall phthalate-free options. This could mean a considerable more amount of time spent in stores or doing research to find those options, however as your health as the consequence, your time spent will be priceless. Also, there are ways to avoid the constant daily use of them, especially with the use of personal care products. In terms of medical devices, I would not personally recommend refusing treatment because of the potential exposure to phthalates until more alternative devices are being provided, have been heavily researched, and deemed safe.

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