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Exposure and Risk Assessment of Phthalates in Women

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ABSTRACT

Phthalates are one of the more favoured plasticisers in polymer industries. The phthalic acid (benzene-1,2-dicarboxylic acid) diesters an artificial substance with a variety of industrial uses, generally known as phthalates. They are of two types: High molecular weight (HMW) phthalates, like DEHP[di(2-ethylhexyl)phthalate], DnOP(di-n-octyl phthalate), and DiNP(di-isononyl phthalate), which are mainly employed in the manufacturing of flexible vinyl to make them more flexible and pliable, and then used to make goods, placemat and wall coverings, applications that come into contact with devices of medical and food. Low molecular weight (LMW) phthalates, those are use in varnishes and coatings, as well as some times releases medicinal preparations, fragrances, moisturizers, and cosmetics. DEP (diethyl phthalate) and DBP (dibutyl phthalate) are the examples of LMW type of phthalate. Exposure to phthalate esters has increased fear of the health and well-being of women. Several noxious exposures of phthalates have been shown to have an adverse impact on health. In the present scenario phthalates exposure has been recognized. However, among the overall human population women are one of the most vulnerable groups, which are often a victim of self-ignorance. Some of the major health issues frequently observed in women due to phthalate exposure are endometriosis, precocious puberty, hormonal disbalance, obesity etc. Although some studies are available concerning the effects of phthalate exposure on women yet major area remains unaddressed. The present review gives insight into the extent of work performed in the above area along with respective loopholes. Also, an attempt has been made to understand the proper mechanism given by simultaneous researchers throughout the globe. Moreover, the study will enable to help professionals in the field to regulate the extent of exposure along with highlighting the alarming situations as a result of phthalate usage and acquaintance.

1. Introduction

Phthalate has been found over a large area of technical uses because of its chemical and physical properties. They are used as anti-foaming agents in paper production, as dielectrics in capacitors, glues, paints and dyes, additives and coatings. They are alsoused to make more durable plastic called plasticizers, especially for the manufacture of different polymers. According to Erythropel et al., (2014), the usage of plasticizers in industrial items such as electronic, automotive, food packaging, textile fibres, and toys has expanded globally in recent decades. To increase the elasticity and toughness of plastic materials, plasticizers are frequently used (Erythropel et al., 2014). According to Erythropel et al., (2014), esters of phthalic acidare often utilised plasticisers because they can increase the ductility and flexibility of polymers. In 2017, accounting for sixty-five per cent of the world's consumption of plasticizers between 2017 and 2022, the total global utilization of phthalates is anticipated to increase at a yearly rate of 1.3% (Markit., 2018). Over four hundred seventy million pounds of phthalate are manufactured and imported each year in the United States. (EPA, 2012).Phthalate estersare liberated into the air throughout the disposal, production storage, or use process since they are weakly bonded to the materials of plastic such as PVC (Starket al., 2005).The principal route of exposureis daily use of the products such as beauty products (Fisheret al.,2019; Nassan et al., 2017: Romero-Francoet al., 2011) toys (Earls et al., 2003), air(Promotes et al.,2019)home furnishings(Carlstedtet al.,2013), cleaning agents, cooking oil etc and mixed into the environment through oxidation, leaching and transmigration (Crinnion, 2010; Heise& Litz,2005; Guo & Kannan, 2012). A past study has shown that the toxicological effect of phthalate esters on human health has increased anxiety on a worldwide scale, so many guidelines have been proposed for the occurrence of phthalate esters in air, water and soil. Diethyl hexyl phthalate,di-n-octyl phthalate, dibutyl phthalate, benzyl butyl phthalate, diethyl phthalate and dimethyl phthalate have been registered as environmental contaminants by theU.S. EPSA 2014 (the United States Environmental Protection Agency)and European Union (Heise and Litz, 2004).

Phthalate has been identified as an endocrine-disrupting compound because it tampers with the hormones present in the human body which seems to be insensitive to the preservation of growth and behaviour, reproduction, and

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homeostasis (Kavlocket al.,1996). According to Mariana et al.,(2016), phthalates can interact with a molecular objective in the body of humans and disturb with balance of hormones, which causesdifferent types of health problems in adults, foetuses, and children(Katsikantami et al., 2016). Esters of phthalic acid have the potential to alter human biological processes and cause cancer, foetal harm, and mutation even at low quantities (Becker et al., 2004; Caldwell et al.,2012).Phthalate analogues containing more than two and less than eight atoms of carbon are development and generative toxins of different potencies, according toHeindel et al., 1989;Gray et al., 2000.DBP (dibutyl phthalate), DEHP (Diethyl hexyl phthalate) have been identified as disruptors of endocrine system based on experimental evidence (Davis et al., 1994a; Corton et al., 1997;Mylchreest et al., 1998; Gray et al., 2000;Lovekamp-Swan and Davis, 2003). These chemicals act through complex routes that typically do not conjoin theoestrogen and androgen receptors. According to research, diethyl hexyl phthalate reduces ovary estradiol synthesis in mature females by preventing the enzymatic aromatase's transcription (Lovekamp and Davis, 2001; Davis et al., 1994a, 1994b). This harms systems that depend on oestrogen, like ovulation and fertilisation(Lovekamp-Swan and Davis, 2003, Adibiet al., 2003; Ema et al., 2000). It is unclear how this oestrogen action can affect a fetus's growth or capacity of a woman to carry a safe pregnancy.In recent decades, concerns about the harmful influence of PAEs (phthalate acid esters) on the development and organs of reproduction have increased. women are far more sensitive to phthalates exposure because they spend approximately 70% of their time indoors. This review seeks to provide a general description of the effects of phthalates on women, as well as their action of mechanism and risk assessment.

2. Classification of Phthalates

According to Saeidnia., (2014), phthalic anhydride and alcohols whose length of chain is in the range of C1 (methanol) to C13 (tridecyl alcohol), are combined to create phthalate esters. Thus, based on the length of their carbon chains, phthalate esters can be separated into two primecategories: high-molecular-weight (HMW) phthalate acid esters with side-chain lengths of 7 to13 carbons and low-molecular-weight (LMW) phthalates with side-chain lengths of 3 to 6 carbons (Table1) (NRC, 2009). Di iso decyl phthalate, Bis(2-ethylhexyl phthalate), Diisononyl phthalate,and di-2-propyl heptyl phthalate are high molecular weight phthalate acid esters that are frequently used in industries to rise the pliability and flexibility of stiff polymers (ECPI, 2014). Additionally, the inclusion of these high molecular weight phthalates has improved the flexibility and tensile strength of manufacturing goods such as flooring, cables, tarpaulin, wires, roofing, wall coverings, and synthetic leather (Wypych et al.,2012, ECPI, 2014, atsikantami et al., 2016).

3. Human's Exposure

Phthalate esters (PAEs) have become a vital group of indoor air pollutants, in the present time (Weschleret al., 2008). It may be present in public places (Weiet al.,2019), houses (Shinohara& Uchino,2020), kindergartens (Raffyet al.,2017), offices and hospitals (Xiaet al.,2018). Submissionof phthalates from home dust and air of indoor may have a remarkable influence on the health ofpersonage. Since most women pass theirmaximum time indoors, where concentrations of plasticized are huge (Luongo and Ostman, 2016; Bergh et al., 2011). Therefore, it is necessary to take into account unintentional dust intake, skin-adhered dust, intake of air and the inhalation dust component as key exposure pathways (Table 2).

People might be in contact with phthalates in a variety of ways. Dermal absorption, such as that caused by diethyl phthalate in cosmetics and other personal care items, dietary or oral ingestion (e.g., Di ethyl hexyl phthalate via phthalate-contaminated water and beverages, food), inhalation (FDA,2001). Phthalates are organic chemicals that are semi-volatile and volatilize from polyvinyl chloride, nail paint, hair spray, and other items containing PAEs products, and parentera. The two primary phthalates in both indoor and outdoor air are diethyl hexyl phthalate and dibutyl phthalate (Jia et al.,2019). Phthalates may seep into packaged goods like bottled water and cooking oil from packaging made of plastic. (Beltifa et al., 2017), fatty foods, milk, beverages, and cookingoil (Qiongetal., 2019;Rastkari et al.,2017; Lin et al., 2015; Guart et al., 2011; Fankhauser-Noti and Grob, 2006).

The use of beauty products is a providing track of women percutaneous, mostly for PAEs of LMW, such as DMP, DEP, DiBP, andDnBP.Wormuth et al., 2006;Guo and Kannan 2013;Koniecki et al., 2011; have detected high concentrations of DEP in deodorants, body lotions, perfume, shampoo, and nail enamels. Cutaneous absorption from air at rates that can be equivalent to intake of inhalation may occur for di-n-butyl phthalate (DnBP) anddiethyl phthalate (DEP) (Weschler et al., 2015; Weschler and Nazaroff, 2014).Gong et al., (2014),assume that the absorption of phthalates (DEP and DnBP) is influenced by skin absorption as well as respiratory intake route.

4. Phthalates metabolism in human's body

When phthalates enter the human body they undergo hydrolysis in two phases, phase 1 and phase 2, before they are emitted from the body through faces, sweat, and urine. (Hineset al.,2009). In step 1, phthalates are hydrolysed Into their primary metabolite monoester phthalates byesterases and lipases in theparenchyma and intestines (Calafatet al.,2006 and Rusynet al.,2006). The subsequent oxidation reactions that the hydrolytic monoester goes through can change the carbon chain. Additionally, glucuronic acid can be used to conjugate the hydrolytic monoester as well as oxidised metabolites that are secondary, which will then be ejected in the urine (Silva et al., 2006a; Silva et al., 2006b; Koch et al., 2006;).DEP, DMP which are low molecular weight phthalate are hydrophilic and their metabolites are mono-methyl phthalates, and mono-ethyl phthalate respectively which are emitted without step2 (oxidation) (Katsikantami et al.,2016). Di-iso-butyl phthalate (DiBP) and di-n-butyl phthalate (DnBP) are primarily released with hydrolyzed monoesters (eighty-four per cent and seventy per cent, accordingly, of the given dosage), and their overall proportion in the urine of humans is around ninety per cent after twenty-four hours oral treatment. The metabolic pathway of high molecular weight phthalate such as DEHP (diethyl hexyl phthalates) is complex because of its branched chain. In the first step of metabolism diethyl hexyl phthalate (DEHP) is hydrolysis to mono ethyl hexyl phthalate (MEHP) catalysed by unspecific lipase (Albro et al., 1986) then MEHP is further oxidized to 5oxoMEHP or 5ox MEPP. Excretions only contain a small percentage of their metabolites, nevertheless. The 24-h-excretion rate falls as the molecular mass of phthalates increases. (Koch et al., 2005).Phthalates and their biochemical routes are explained in Figure 1. Presently, PAEs have been found saliva, breast milk, amniotic fluid, in the circulatory system and semen

(Kim et al., 2015b; Katsikantami et al.,2016; Lin et al.,2016; Wang et al.,2016a; Jornet-Martínez et al., 2015; Ashley-Martin et al., 2014). Furthermore, phthalates were discovered in foetal meconium (Li et al., 2013) and adipose of adult tissue connected to the hair of humans at low levels (Chang et al., 2013).

5. Effect of phthalates on human's body

Phthalates do not have any covalent bond to the polymer molecules. Due to its ease of extraction and environmental pollution, human beings are more likely to have negative health impacts. This figure 2 shows the possible mechanism how phthalates affect human's health by causing several diseases in both men and women (Golestanzadeh et al., 2020). Phthalates have both genomic and non-genomic effects (Jiaet al.,2019).The genomic effect causes hypermethylation, hypomethylation and aromatase etc (Duttaet al.,2020).

5.1 Obesity

Obesity is speedily spread all over the world. When humans come in contact with phthalates, such as DINP, and DEHP in early years may cause to increase in weight and obesity. Endocrine-disrupting chemicalsare also known as obesogens.Obesogens can encourage adipogenesis and contribute to an increase in weight (Apauet al.,2020).Obesogens are compounds of chemicals such as phthalates that are used in the construction of the body's fat cells. Phthalates can enlarge or multiply fat cells within a person's body.This can cause an increase in the mass of the body. Approximately forty per cent of cosmetic products have phthalates (Halden et al.,2010).Phthalates especially Di(2-ethylhexyl) phthalate has been known to contribute to the high dissemination of various indication including obesity. Di (2-ethylhexyl) phthalate exposure may possess body weight change. So, the relationship between obesity and phthalate exposure has been broadly studied in several populations (Xiaet al.,2018). According to World Health Organisation (WHO), this may define by using BMI, the full form of BMI is Body Mass Index. Here use (BMI = weight/height2) to determine obesity in humans. A human with a body mass index between thirty and thirty-four point nine-nine is considered to be category one obese, and between thirty-five and thirty-nine point nine-nine is considered to be category two obese and above forty-class three obese (WHO 2000). In teenaged and kids, a nomogram is utilised to detect if one is obese or not. Obesity isexplained as having a body mass index that is at or above the 95th percentage point for one's age as well as gender (Weiner et al., 2016). According to the new government survey, Indians are getting fatter. In India, obesity could soon become widespread if we don't aware of it. The bellow chart shows how speedily obesity spread in India in the last few years (NFHS-4 2015-16 and NFHS-5 2019-21)

5.2 Diabetes

DEHP, a plastic additive, is allied with a high dispersal diabetes mellitus type 2 (T2DM) (Dinget al.,2021). Testimony has verified that DEHP in the atmosphere is related to the dispersal of pubertal (T2DM) type 2 diabetes mellitus (Radkeet al.,2019). Metabolic and endocrine disorder T2DM has spread globally (Dinget al.,2021). As specified by IDF (International Diabetes Federation) the number of diabetes victims reached an astonishing number of four hundred sixty-three million in 2019 with a prediction of around five hundred seventy-eight million in 2030 and seven hundred million in 2045 (Saeedi et al.,2019). Research has demonstrated that the risk factors for diabetes mellitus type 2 (T2DM) incorporate factors of genetic, environmental and behavioural. Environmental pollutants such as di ethylhexyl phthalate, PM1.0, heavy metals and PM2.5 play an important role in the spreading of diabetes mellitus type 2 (T2DM) (Dendupet al.,2018). It has been found that exposure to DEHP could affect the development of T2DM. In T2DM patients, exposure to DEHP raised inflammatory levels as well as oxidative stress and lowered levels of adiponectin. (Duanet al.,2017). Phthalate affects glucose homeostasis and hormonal status. Phthalate submission can cause insulin resistance and oxidative stress as probable type 2 diabetes mechanisms (Daleset al.,2018). For type 2 diabetes phthalates exposure effect more middle-aged women as compared to older women (Sun et al.,2014). The estimation in 2019 showed that 1 in 6 people suffering from this disease belongs to India. Among the top five countries, India got the second position in diabetes (Pradeepa and Mohan, 2021).

5.3 Respiratory diseases

Phthalates found in food, dust and air, may further cause breathing diseases such as chronic pulmonary disease (COPD) and asthma in women. Many studies have shown positive relationships between phthalate (DBP, BBP, MEHP) and respiratory diseases (Kuet al., 2015;Baleet al.,2020). Allergic rhinitis is a generic upper respiratory disease. The common signs of this disease are nasal itching, sneezing, nasal congestion and running which may be included irritation in the eyes. It is possessing 10% - 40% of the world's community, decreasing the quality of life (Brożeket al.,2017).The pathogenetic of allergic rhinitis is complicated, and hereditary and environmental factors play a crucial role. In recent years, environmental factors have taken centre stage. The study discovered that a variety of allergy disorders are closely associated with air pollution and environmental endocrine disruptors (EDCs), two sources of environmental pollution that are of great concern globally. The most prevalent phthalate, DEHP, is a type of EDC that can enter the human body by breathing and water consumption and has harmful effects on the breathing system. The effect of phthalates on the respiratory system has gained attention in recent years. According to several research, DEHP may be linked to asthma and allergy symptoms (De Coster & Van Larebeke, 2012). According to Larsen et al., (2007), Di(2-Ethylhexyl) Phthalate (DEHP) may encourage a dissipated asthmatic condition and pathologic lung tissue alterations.

5.4 Coronary heart disease

The leading cause of mortality worldwide is heart disease. Increasing laboratory testimony indicates that exposures to phthalates early in life may disturb constantly disturbing metabolic pathways, developmental endocrine processes and promoting to adverse cardiovascular profiles (Trasande and Attina., 2015). The correlations between phthalate exposure and circulatory heart diseases have been observed, as have coronary heart illness (Jaimes III et al.,2017). On the report of the World Health Organization (WHO), coronary heart diseases are the chief reason of death worldwide. The impact of different types of pollutants on health of the women has also been introduced as a factor for cardiovascular diseases, with numerous research have suggested a link between PAEs and cardiovascular diseases (Suet al.,2019). DEHP is capable of clinging to airborne dust particles before falling back to Earth. According to Wang et al., (2019), phthalates are easily absorbed by humans through ingestion, inhalation, and skin contact with phthalate-contaminated items. Some researchers suppose that the risk of cardiovascular disease expands as the amount of PAEs

increases (Olsenet al.,2012).The HMW phthalate DEHP (di-2-ethylhexyl phthalate) has been linked to elevated blood pressure (Mariana et al., 2016). The existence or lack of echogenicity of plaques, echogenicity of the intima-media complex, intima-media thickness of the typical carotid artery, and overt atherosclerotic plaques were associated with the MEHP phthalate concentration (Lind, P. M., & Lind, L., 2011). Di ethyl hexyl phthalatehasbeen identified as an initiating and escalating risk factor for cardiovascular disease. Through its chemically active metabolites, which mostly contain MEHP, DEHP is a precursor that aids in the pathogenesis of heart disease (Wen et al., 2022). (figure 3).

A prospective birth cohort of low-risk pregnant women was recruited for the health outcomes. Also,mono benzyl phthalate concentrations have been related to the jeopardy of pregnancy-operated disorders of hypertension (Werner et al., 2015). The phthalate-associated hypertension may be connected to the raised plaque echogenicity, intima-media thickness, and the echogenicity which are more probable to develop in people who are exposed to phthalates (Lind and Lind, 2011).

Phthalates and cardiovascular risk factors are related; however, the evidence is of low-high quality. This is because phthalates have brief physiologic half-lives; as a result,information on long-term exposure cannot be obtained from the single measurement used in the majority of investigations. Additionally, it is difficult to compare the detection of different studies because phthalates have a wide range of metaboliteandthe researchers that conducted phthalate studies did not examine the effects of the same metabolites. Additionally, the majority of the research is based on pharmacovigilance studies or population-based surveys, i.e., studies that weren't intended to explore how phthalates affect cardiovascular risk factors (table 3).

5.5 Liver Toxicity

The liver is a multicellular organ that is a complicated tissue. For tissue homeostasis to be maintained in terms of repair, renewal and regeneration as well as for liver function, complex and structured interactions are essential.The majority of the liver's cells, or hepatocytes, perform specialised critical processes suchas detoxification, protein synthesis,carbohydrates and the metabolism of lipids. Hepatocytes account for 50–80% of the liver's mass.(Berardis et al.,2014; Fausto&Campbell,2003; Huchet al.,2013). The appropriate activation and differentiation of liver stem proliferation, and progenitor cells into maturebile duct cells and hepatocytes during the chronic liver injury is crucial (Sadriet al., 2016). As a result, chemically induced disruptions of liver stem and progenitor cells' capacity for regeneration can interfere with tissue homeostatic processes, which in turn can affect the onset and intensity of chronic livertoxicities. The quantity of diethyl hexyl phthalate for the risk of raised mass of the liver in adolescents and females of reproductive age is twenty g/kg-day, on the statement of the U.S. EPA (United Environmental Protection Agency States,2020). When considered as a whole, the liver is an organ that is negatively impacted by exposure to phthalates and their effects on health. In Shuman blood plasma or serum, concentrations of a few specific phthalates (DEP, DEHP, DBP, and BBP) frequently vary from 0.001-0.5 mg/L (Hogberg,2008; Wan, 2013; Chen 2008, Kim, 2011, Reddy, 2006) with even higher mean levels (0.2-4.4 mg/L) recorded for certain people, such as Asian women with endometriosis in severe phases (Kimet al.,2011;Reddy et al.,2006).According to tveráková et al.,2020 phthalates may also affect liver oval cells or liver stem and progenitor cells through non-genomic pathways. Gap junctional intercellular communication and the signalling pathway for mitogen-activated protein kinases are important mechanisms for the upkeep of liver tissue homeostasis. Hepatotoxicities caused by phthalates and the potential emergence of chronic liver disorders like liver cancer may be related to the disruption of these systems in the essential growth of liver oval cells. Hepatocytes are the target cell populations for PAEs tumour-promoting and liver-toxic effects, but the majority of research has focused on genomic signalling as the primary mechanism and hepatocytes or hepatoma cell lines as the subject cells for these effects (Pham et al., 2016). Non-genomic processes in liver oval cells and cellular models require more study.

The correct activation, proliferation, and differentiation of progenitor cells andliver stem into mature hepatocytes and bile duct cells are essential throughout chronic liver injury. (Canovas-Jordaet al.,2014; Kanget al.,2011;Knightet al., 2007; Persanoet al.,2015; Vanovaet al.,2019;Wang&Sun, 2018; Vondráˇcek et al.,2016). At the beginning of carcinogenesis, liver stems and progenitor cells probably multiply and may give rise to hepatocytes that become cancer progenitors (Fausto & Campbell, 2003).

5.6 Endometriosis

An increasing amount of evidence has shown that phthalates may have had a role in the aetiology of endometriosis over the past decade. Fifteen per cent of women of reproductive age have endometriosis, making it one of the most prevalent illnesses (Houstan et al., 1987; Kirshon et al., 1987; Cramer & Missmer., 2002). Dyspareunia, persistent pelvic discomfort, dysmenorrhea, and menorrhagia—all of which can result in infertility—are addressed (Melis et al., 1994; Parazzini et al., 1999; Reddy et al., 2006). Numerous research has suggested associations between PAEs exposure and the chance of emerging endometriosis. Although it's not entirely clear how phthalates affect endocrine-related diseases in women of reproductive age. When endometrial-like tissue appears on the uterine surface or frequently in the peritoneal cavity, endometriosis is a serious disorder. Endometriosis affects between 6–10% of childbearing-age women(Eskenazi&Warner,1997).Infertility, ovarian cancer, ovarian cysts, pelvic discomfort and hormonal issues with the peritoneal cavity and endometrium can all result from this condition, which is brought on by the unexpected development of tissue outside the uterus (Upsonet al.,2013). Phthalate exposure may cause the installation of endometriosis by increasing proliferative activities and invasive activities of endometrial cells. According to several studies, women with endometriosis were more likely than women without the condition to be exposed to endocrine-disrupting chemicals (EDCs), such as diethyl hexyl phthalate and di-n-butyl phthalate metabolites. Although some researchers hypothesised that diethyl hexyl phthalate boosts endometrial cells' viability, which might result in the proof of endometriosis.According to Tsatsakis et al.,(2019), women who are in contact with these phthalates havefewer testosterone levels, are more likely to become pregnant, and have a lower risk of PCOS (polycystic ovarian syndrome). Phthalates may be linked to the development of endometriosis given the increased levels of these compounds in the plasma of endometriosis patients compared to fertile controls. Further research is required to identify the genes and factors that contribute to the aetiology of endometriosis because it is a condition that is extremely poorly understood.

5.7 Ovarian dysfunctiony

Monoethyl phthalate (MEP), monobutyl phthalate (MBP), in women of reproductive age were over twelve and two hundred times higher, as compared to the men (Hernandez-Diaz et al.,2013). Women have more exposed to phthalate than men. Females have higher concentrations of MEHP, MBzP, MBP, and MEP than males (Silva et al.,2004). Unsurprisingly, among all sexes and age groups, women who are childbearing age have the maximum exposure to MBP (monobutyl phthalate) (Blountet al., 2000). These findings are most likely related to the ubiquitous cosmetic and personal care products used by females on regular,lotion,nail polish hairspray, and perfume, which contain phthalates, particularly MBP.Messerlianet al., 2016; Toft et al.,2012 & Ferguson, K. K.et al.,2014 studies indicate that phthalates affect female reproductive health. The amount of phthalate in women has been linked to defects in folliculogenesis and steroidogenesis can cause reducedpregnancy rate, non-reproductive disorder, increased rates ofpregnancy complications, miscarriages, infertility and diminished ovarian reserve.With an emphasis on the effects of phthalates on folliculogenesis and steroidogenesis. Few research has examined how phthalates affect follicle development, however, there is evidence that suggests phthalates impact follicle development and function at different phases of the process. Phthalates specifically have been demonstrated to influence ovarian and oocyte development, disrupting the initial phases of folliculogenesis. Oocyte formation has been demonstrated to be inhibited by diethyl hexyl phthalate exposure during sexual development (Kim et al., 2002).

For both reproductive and non-reproductive health, ovarian steroidogenesis must be properly regulated, and various studies show that phthalates can dysregulate steroidogenesis in a variety of ways (Fig. 3). Particularly, it has been demonstrated that PAEs interfere with the synthesis and emission of several sex steroid hormones in vitroas well as in vivo systems, frequently resulting in a drop in estradiol levels. Additionally, it has been demonstrated that phthalates directly target a number of steroidogenic cell types in the ovary to have a negative impact on the generation of steroid hormones (Panagiotou et al.,2021). All aspects of the female reproductive system taken into account in order to comprehend how phthalates affect female fertility, and the methods by which phthalates disrupt the hypothalamus-pituitary ovary axis must be discovered. Because phthalates are found in mixes, it is necessary to evaluate a variety of individual phthalates to see whether they all represent comparable risks.

5.8 Breast Cancer

Breast cancer affects 2.1 million women annually and accounts for roughly 15% of all female fatalities, as reported by the WHO (WHO 2020) (Rojas and Stuckey, 2016). Breast cancer is a complicated condition that is influenced by a number of various factors, such as PAEs, pesticides, C_6H_5OH, Hg, etc. (Brody et al., 2007; Winters et al., 2017). Diesters of, PAEs are potentially endocrine disruptors. The synthesis,transport, secretionand binding of endogenous hormones can be affected by endocrine disruptors (Quagliariello et al., 2017). According to Quagliariello et al., (2017), phthalate esters are recognized to promote cell proliferation, angiogenesis, alterations in programmed cell death, and other effects that might result in the evolution of hormone-dependent cancers like breast or prostate cancer. An endocrine disruptor may also give cancer cells chemoresistance. It has been observed that PAEs or 4,4'-(propane-2,2-dial)diphenoltrigger the release of pro-inflammatory factors when patients are administered the anthracycline anticancer medication doxorubicin. These pro-inflammatory components can lead to doxorubicin-induced cardiotoxicity and chemoresistance (Chatterjee etal.,2019; Quagliarielloetal.,2017).

Approximate 2 million tons of phthalates produce yearly and tend to be well-known cancer-encouraging agents (Hauser et al., 2005; Winters et al., 2017; Lopez-Carrillo et al., 2010; Hsieh et al., 2012; NicolopoulouStamati et al., 2015; Rowdhwal and Chen, 2018). Females frequently develop hormone-related breast cancer, and the propensity of PAEs to act as endocrine disruptors put women in danger. Multiple glandular organs that are part of the endocrine system produce hormones in the bloodstream. The production, secretion, transport, action,clearance of hormones and binding are known to be disrupted by endocrine disruptors, which may further impair female development(Macon and Fenton, 2013).Phthalates may have an impact on the tumour cell's microenvironment. The microenvironment is crucial to the development of any malignancy. The Lopezcarillo et al., and Ahern et al., (2019)study discovered a connection between phthalates and breast cancer and demonstrated how diethyl phthalate (DEP) and mono ethyl phthalate (MEP), cause cancer in pre-menopausal women. Similarly, to this, Zhang et al.,(2016) discovered that DEHP exposure increased the invasiveness of MDA-MB-231 breast cancer cells. Furthermore, a well-known study by Kim et al.,(2004) further demonstrated that PAEs, such as DEHP, BBP, and DBP, promote cell growth in an estrogen-positive breast cancer cell line. The same research team's subsequent investigation further showed that treating cells with phthalate before giving them tamoxifen and a breast cancer treatment medicine lowers the mortality of the cell line (Mughees et al.,2022). Future studies can be focused on utilising cutting-edge increase, genomics, and in-silico methods to identify other potential cellular targets and ways that will reveal the full structure of the progression of disease caused by PAEs in humans. This element, despite being a fascinating and significant research problem, had not been addressed in the proper manner.

6. Health Risk Assessment

As analytical statistical techniques,the Pearson product-moment correlation and the Mann–Whitney U-test (Olsen et al.,2012) also known as Spearman rank correlation was used. Leve'ne and Kolmogorow-Smirnow tests were used to check for normal homogeneity and distribution. Some other statistical tools as SPSS (Mariana et al., 2016), R, SAS (Lind et al., 2011) and MATLAB (Olsen et al.,2012) for understanding the impact of phthalates in air. Thermal Desorption and NIOSH are technical methods for the determination of phthalate. The thermal Desorption technique is best for the detection of phthalates in air. In this technique sample reports to the GC-MS system. In the thermal desorption technique, a wide spectrum is obtained from the group of phthalates in small quantities. All the steps involved are automated. In the below table.4 some models' names and effects of phthalates were described.

6.1 Calculation for the inhalation exposure concentration (EC_{inh})

$$EC(\mu g/m^3) = \frac{C \times ET \times EF \times ED}{AT}$$

Where,

ED = =Exposure Duration

EF = Exposure Frequency
AT = Average Time
ET = Exposure Time
C = Concentration

6.2 Risk Assessment using Quantify Hazard Quotient (HQ)

HQ = EC/Rfc

Where,
EC = Exposure Concentration
Rfc = Reference concentration of Particulate Matter

6.3 Lifetime Average Daily Dose (LADD)

$$LADD = \frac{(CA \times IR \times ED \times EF)}{BW \times AT}$$

Where,
AT = Average Time (days)
IR = Inhalation Rate (m^3/h)
EF = Exposure Frequency (days/ years)
ED = Exposure Duration (years)
CA = Contaminant Concentration ($\mu g/m^3$)
BW = Body Weight (Kg)

6.4 Excess Lifetime Cancer Risk (ELCR)

$$ELCR = SF \times LADD$$

And,

$$SF = UR/BW \times IR$$

Where,
SF = Slope Factor
UR = Unit Risk ($\mu g/m^3$)
BW = Body Weight (Kg)

7. Conclusion

The present review focused on the phthalates, its classification, uses and extent of women's health outcomes allied with phthalates. Women are more prone for its toxicity because phthalates are found in air fresheners, household products, food and liquid container, cosmetics, personal care products and perfume. Phthalate is an endocrine-disrupting chemical with an undesirable effect on women's health likeobesity, diabetes, thyroid diseases, kidney diseases respiratory diseases, cardiovascular diseases, and other reproduction system-related diseases in women.Future research needs to be rigorously carried out by using more sample sizes to find logical and positive results for understanding the overall effect of phthalate on women's health.Studies are required to find out the

1-Effect of phthalates and female reproduction function (that is, semen quality assessments and menstrual cycle, as well as measures of fecundity and fertility).

2-Women exposed to obstructive airway and asthma.

Table 1. Phthalates and their metabolites

Compounds	Abbreviation	Category	Primary metabolites	Secondary metabolites	Chemical formula
Diethyl phthalate	DEP	LMW	MEP	-	$C_{12}H_{14}O_4$
Dimethyl phthalate	DMP	LMW	MMP	-	$C_{10}H_{10}O_4$
Di-isobutyl phthalate	DiBP	LMW	MiBP	2OH-MBP and 3OH-MiBP	$C_{16}H_{22}O_4$
Butyl-benzyl-phthalate	BBzP	LMW	MBzP	MCPP	$C_{19}H_{20}O_4$
Di-2-ethylhexyl phthalate	DEHP	HMW	MEHP	MECPP, MCMHP, MEHHP, MEOHP	$C_{24}H_{38}O_4$
Di-iso-nonyl phthalate	DiNP	HMW	MiNP	MCiOP, MHiNP, and MOiNP	$C_{26}H_{42}O_4$
Di-n-hexyl phthalate	DnHP(low or high)	LOW OR HIGH	-	-	$C_{22}H_{34}O_4$

Table 2. Concentration of phthalates (ng/m3) in different microenvironment

Place	DEHP	DBP	DEP	BBP	DiBP	References
Outdoor air (USA)						
Small town	<LOD-309	3-156	<LOD-234	<LOD-48	6-226	Tienpont,2004
Highly industrialized area	<LOD-333	_	4-70	_	-	Peijnenburg,2006
Road area	<LOD-34	4-93	<LOD-81	<LOD	8-101	Tienpont,2004
Underground parking	228-1046	84-946	57-224	<LOD-26	62-314	Peijnenburg,2006
Indoor air (USA)						
Home	110	410	350	35		Sheldon,1992
Office	100-200	50-780	-	-	-	Tienpont,2004
Commercial area (carpet shop)	96	294	158	192	9445	Tienpont,2004

***LOD is the limit of direction**

Table 3. Effect of Phthalates on Cardiovascular Diseases

Sr No.	Reproductive	Phthalates	Effects	Reference
1.	Female	MMP	risk of coronary heart disease	Olsenet al., 2012
2.	Female	MEHP	The echogenicity of vascular plaques	Lind, P. M., and Lind, L., 2011.
3.	Female	DiNP and DiBP	Increased blood pressure	Trasande and Attina, 2015.
4.	Female	MBzP	pregnancy-induced hypertensive diseases, Increased diastolic blood pressure	Werner et al.,2015

Table 4. Models name for the detection of the association of phthalates

Serial No.	PAEs and metabolites	Location	Type of Study	Population	Model	Effect on health	Association		References
1.	BBzP MBzP	Taiwan	Longitudinal cohort	208 mother-baby couples	Logistic regression	Associated with ADHD in children	OR = 9.12 (95% CI: 1.07–78.06), p < 0.05	(+)	Ku et al. (2020)
		USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models	Associated with higher scores for oppositional behaviour	RC = 0.16 (95% CI: 0.01, 0.32	(+)	Kobrosly et al. (2014)
2	DiBP MiBP	USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models	Associated with higher scores for conduct problems	RC = 0.39 (95% CI: 0.20, 0.58)	(+)	Kobrosly et al. (2014)
		USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models	Associated with higher scores for inattention	RC = 0.27 (95% CI: 0.04, 0.50)	(+)	Kobrosly et al. (2014)
		USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models	Associated with higher scores for aggression	RC = 0.34 (95% CI: 0.09, 0.59)	(+)	Kobrosly et al. (2014)
		USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models.	Associated with higher scores for rule-breaking behaviour	RC = 0.20 (95% CI: 0.01, 0.38)	(+)	Kobrosly et al. (2014)
3	ΣDEHP	Taiwan	Longitudinal cohort	208 mother-baby couples	Logistic regression	Associated with ADHD	OR = 3.28 (95% CI: 1.15–9.35), p < 0.05	(+)	Ku et al. (2020)
		USA	Longitudinal cohort	153 mother-baby couples	Adjusted multiple regression interaction models	Associated with higher scores for somatic problems	RC = 0.15 (95% CI: 0.03, 0.28)	(+)	Kobrosly et al. (2014)
	MEHHP	Taiwan	Longitudinal cohort	208 mother-baby couples	Logistic regression	Associated with ADHD	OR = 2.98 (95% CI: 1.05–8.48), p < 0.05	(+)	Ku et al. (2020)

Notes:
OR = odds ratio
CI: confidence interval
RC = regression coefficient
(−): no association
(+): positive association
(β = beta coefficient)
Where,
ADHD= Attention-deficit/hyperactivity disorder
SF = Slope Factor

Table 5. Health Risk Assessment Data

Factors	Value	Reference
Inhalation Rate	14.25 m^3/day	Jang et al.,2014
Body Weight	62.8 Kg	Jang et al.,2014
Exposure Duration	24 hrs	Greene et al.,2006
Average Time	70 Years	Greene et al.,2006
Exposure Frequency	365 days/years	Zhang et al.,2012

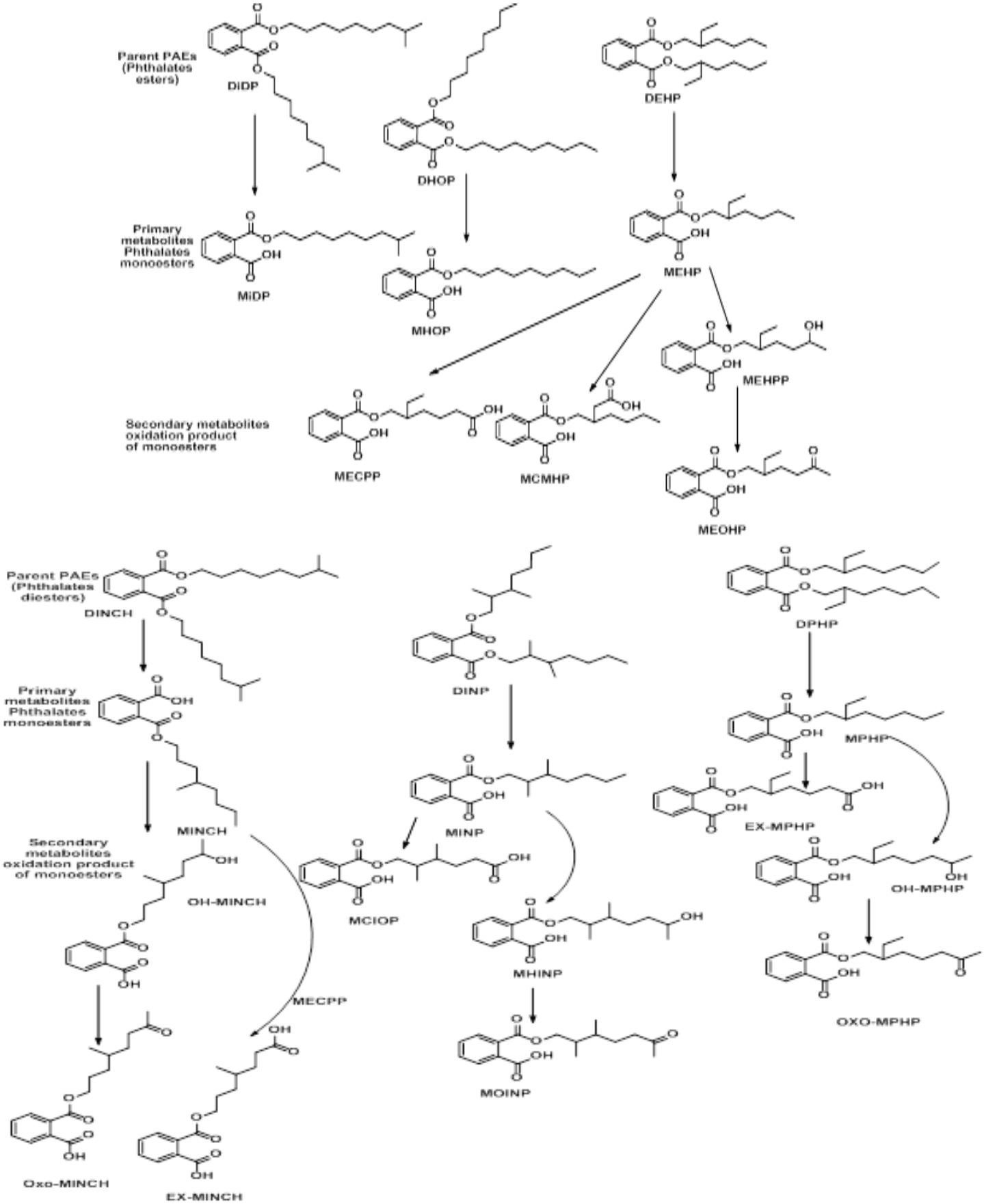

Figure 1. Metabolism of High molecular weight phthalate

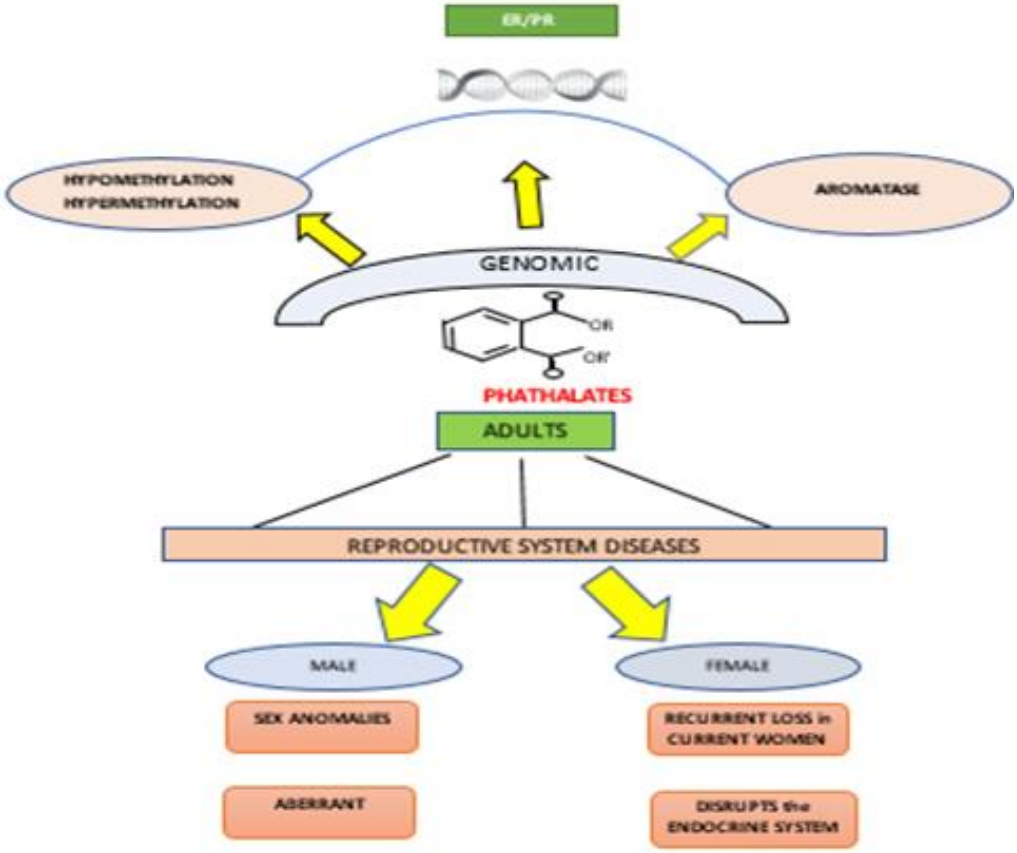

Figure 2. The Mechanism of Epidemiological

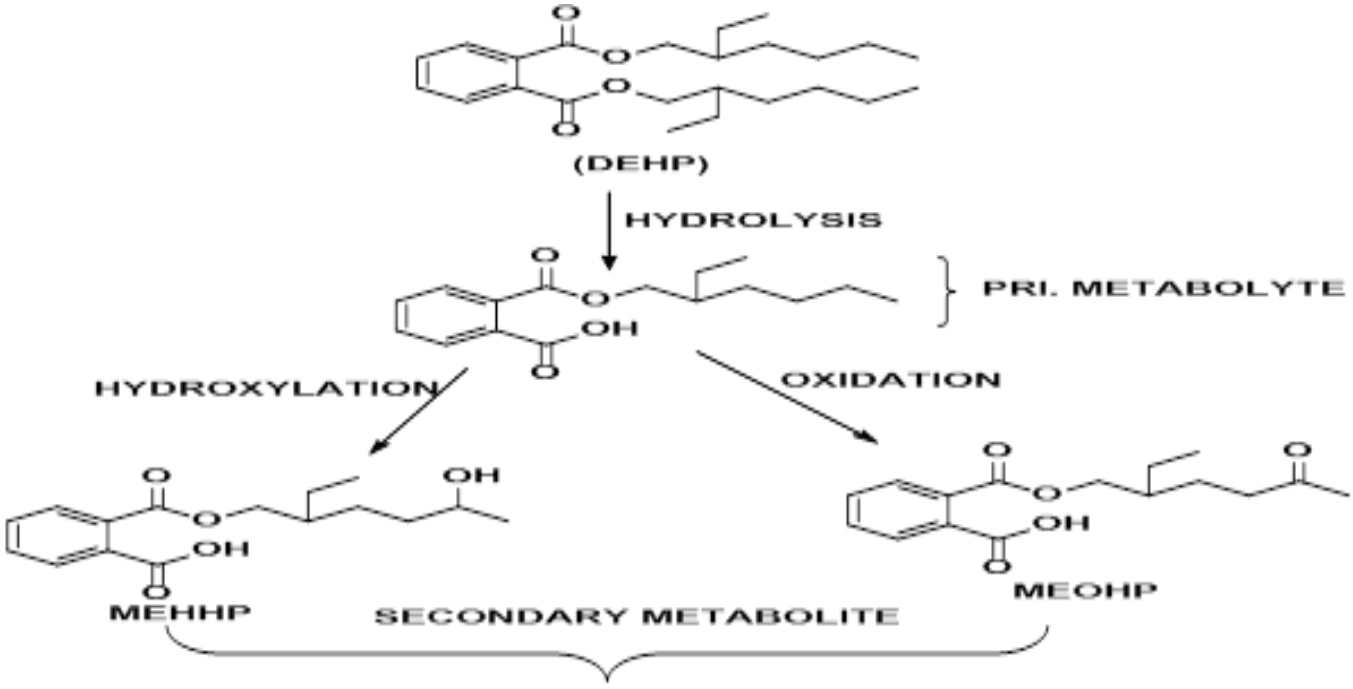

Figure 3. Pathway of Diethyl hexyl phthalate in the human body

*MEHP= Mono (2-ethylhexyl) phthalate
*MEHHP= Mono (2-ethyl-5-hydroxy hexyl) phthalate
*MEOHP= Mono (2-ethyl-5-oxohexyl) phthalate

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