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A Comparative Study of Phthalates in Short and Long Term Plastic using Women Volunteers by GCMS and HPLC Analysis

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KEYWORDS

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ABSTRACT:

Introduction: The usage of plastic products had been multiplied several folds in past few decades. Products which are used on day-to-day life viz shampoos, talcum powders, perfumes, nail polish, toys, cooking materials and etc. contain phthalates. Most phthalates are commonly exposed to the general population through food and water consumption and also, they can enter a person's body through inhalation or skin contact and these metabolites have been linked to a number of major health issues, including endocrine disruption.

Objectives: As there are only a very few studies in human beings with regard to the metabolites of phthalates in blood, this study focuses on the comparison of level of phthalate esters in short term and long-term plastic using women.

Methods: Questionnaires were circulated to 2500 women volunteers of reproductive age group ranging from 20-45 years. Based on their age and exposure to plastic products woman participants are categorized in to two groups, Group I-Short term exposure to plastics aged 20-32 years and Group II - Long term exposure to Plastics aged 33-45 years. The presence of phthalates was analyzed using GC-MS and the levels of phthalates were further quantified using HPLC for both the groups.

Results: The results were expressed as mean ± standard deviation (SD). Statistical differences among controls and each test group were determined by using one-way analysis of variance (ANOVA). $P<0.05$ was considered statistically significant. When ANOVA resulted in a statistically significant value, a post-hoc test, Tukey, was performed and significant increase was observed in long term plastic users. Results on quantification of phthalate shows the significant differences in the concentrations of phthalate esters in between the group I and II. However, among the identified phthalates, DMP, DEP, DINP, DONP and DBP were below their quantification limit in the case of group I, whereas in the case of group II, all the 9 phthalates (DMP, DEP, DBP, DHP, BBP, DBEP, DEHP, DINP and DNOP) being detected. From the results we inferred that majority of phthalates residues showed a remarkable indication in group II advanced age, whereas three main low molecular weights phthalates such as Diethyl phthalate (DEP), Dimethyl phthalate (DMP) and Di butyl phthalate (DBP) showed their indication in group I when compared with group II.

Conclusions: In comparing short term and long-term plastic using women volunteers, the blood samples of long term volunteers showed increased amount of DMP, DEP, BBP and DEHP metabolite. Hence this study recommends the avoidance of usage of plastic products wherever possible and to use alternate to plastics. Phthalates containing cosmetic products should be replaced with natural and herbal products

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1. Introduction

Plastics are used in thousands of household products for convenience and comfort. They are composed of monomers held together with plasticizers viz phthalate esters. Globally, around six million metric tons of plasticizers are consumed every year [1] as they are used in a lot of different things, like enteric coatings for pharmaceutical pills, shampoos, perfumes, nail polish, plastic toys, building materials, nutritional supplements, gelling agents, film formers, stabilizers, dispersants, lubricants, binders, emulsifying agents, and suspending agents, agricultural adjuvants, building materials, personal hygiene products, medical devices, detergents, surfactants, packaging materials, modelling clay, waxes, paints, printing inks, coatings, food products, textiles adhesives , glues, chalk, soft plastic fishing lures, and other plastic products. Phthalates are also present in cosmetics such as eye shadow, perfume, and other personal care items. [2,3].

Several pathways exist for phthalate exposure in humans and can enter a person's body through inhalation, ingestion and skin contact. The human body quickly converts phthalate esters into monoesters, which are then further oxidized to form oxidative metabolites which might cause major health issues, including endocrine disruption, reproductive, developmental damage, and lung allergies [4].

Due to the high level of exposures associated with taking these medications, especially in sensitive populations including pregnant women and children, DBP in medications raises concerns about health hazards [5] Dibutyl phthalate (DBP), di-2-ethylhexyl phthalate (DEHP), and diisobutyl phthalate are three phthalates that are categorized as reproductive toxicants [6].

2. Objectives

The usage of plastics is invincible in past few decades and the plasticizer which are used as crosslinking agents in plastic products which possess the property of leaching and entering in to the biological system. This study aims to find the relationship between the exposure period and the presence of Phthalate metabolites in blood in women volunteers of short term and long term plastic exposure.

- To circulate the questionnaire to categorize women participants based on their plastic exposure relating to age.
- To detect and identify the phthalates in blood by Gas chromatography and Mass spectroscopy.
- To quantify the amount of phthalate esters via HPLC in experimental groups

3. Methods

Ethical clearance for the following was sought from ARC Fertility Centre's Institutional Ethical Clearance Board and received (ARCIEC/others/002/2021).

A questionnaire was circulated to 2500 women volunteers in age range of 20-45 years with consent. Based on their age and exposure to plastic products, woman participants are categorized in to two groups

Group I: Short-term exposure to plastics/plasticizers 20-32-year-old women. (30 women participants were selected.

Group II: Long-term exposure to Plastics/Plasticizers 33-45-year-old women as group II (30 women participants were selected)

Blood Sample Collection

5 ml of the whole blood samples were collected from each women participant in a vacuum glass tube by venipuncture with vacutainer blood collection equipment using stainless steel needles that were screwed into the vacutainer one-use holder. The 10 mL glass vacutainer was directly inserted into the holder and into the back end of the needle. The collected blood samples were transported in a cooling pail and centrifuged at 3000 rpm for 15 mins within 24 hours of collection. The serum was kept frozen in a glass vial at -80°C in a deep freezer until the phthalates were analyzed.

Gas Chromatography-Mass Spectrometry (GC-MS)

GC-MS is an analytical method used for identifying different types of phthalates present in the sera. The frozen serum samples of the test groups (Group I and Group II) were pretreated and extracted for the analysis of phthalates. A GC-MS was performed on Shimadzu GCMS-QP2020 ultra equipment equipped with a mass selective detector. For the analysis, the initial oven temperature was set to 100°C with a duration of 1 min and a following ramp of 10°C/min until 260°C, targeting 320°C with a duration of 2 minutes. The injector, transfer line, and ion source temperatures were held at 260°C, 280°C, and 230°C, respectively. Extracted sample volume of 2 μL was injected spotlessly on the GC

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inlet. Mass spectra were acquired with a scan range of 25-500 m/z. The identification of components was based on Willey and NIST libraries as well as a comparison of their retention indices. The constituents were identified after comparison with those available in the computer library (NIST and Willey) attached to the GC-MS instrument, and the results obtained have been tabulated.

High-performance Liquid Chromatography Analysis

The concentration of the phthalates identified from GC-MS was further quantified by using HPLC. This method embraced sample pretreatment, solid-phase extraction, and instrumental analysis. For all detection and quantification of phthalates, HPLC was used.

Statistical Analysis

For statistical data analysis, continuous variables were expressed as mean ± standard deviation (SD). Statistical differences among controls and each test group were determined by using one-way analysis of variance (ANOVA) statistics. $P<0.05$ was considered statistically significant. When ANOVA resulted in a statistically significant value, a post-hoc test, Tukey, was performed. Values in figures are mean ± SD.

.**Results**

Detection and Identification of phthalates in serum by GC-MS chromatography

Gas chromatography-mass spectrometry (GC-MS) is the preferred method for phthalate identification due to the high reproducibility and specificity. Full scan acquisition and selected ion monitoring were used to simultaneously detect the phthalates and to provide sufficient sensitivity for their identification and/or confirmation. Individual phthalates were identified by comparison of their retention times (RT) and mass fragmentation patterns, the m/z range of 40–400 was selected to include the phthalate fragment ions with the highest molecular weight and to exclude fragment ions with high and low molecular weight.

In our studies 30 test samples from Group I, 30 test samples from Group II shows the chromatogram in selection ion monitoring (SIM) mode for phthalates investigated. As shown, they were detected in less than 14 minutes. Table 1 shows the molecular weights, Molecular formulas, fragment ions (*m/z*) and retention times for each phthalate and internal standard. Benzyl benzoate (BB) was used as internal standard and also the most prominent masses of this compound were selected from the chromatogram in scan mode. GC- MS spectra was recorded to identify the phthalate residues present in the samples.

Table 1. GC-MS analysis, molecular weight, molecular formula, product ion and retention time (RT) for nine phthalates.

Phthalate	Molecular Weight g/mol	Molecular Formula	Product ions (m/z)	RT (min)
Dimethyl phthalate (DMP)	194.18	$C_{10}H_{10}O_4$	1,67,192	6.5
Diethyl phthalate (DEP)	222.24	$C_{12}H_{14}O_4$	149 ,177	7.08
Di n-butyl phthalate (DBP)	278.34	$C_{16}H_{22}O_4$	149, 205	8.43
Di hexyl phthalate (DHP)	334.45	$C_{20}H_{30}O_4$	1,49,222	9.67
Butyl benzyl phthalate (BBP)	312.36	$C_{19}H_{20}O_4$	1,49,207	9.75
Bis (2-n-butoxyethyl) phthalate (DBEP)	366.45	$C_{20}H_{30}O_6$	1,49,199	10.09
Bis (2-n-ethylhexyl) phthalate (DEHP)	390.56	$C_{24}H_{38}O_4$	1,49,279	10.32
Di-n-octyl phthalate (DNOP)	390.56	$C_{24}H_{38}O_4$	1,49,261	11.02
Dinonyl phthalate (DiNP)	418.61	$C_{26}H_{42}O_4$	1,49,222	11.86
Benzyl benzoate (BB) Standard	212.24	$C_{14}H_{12}O_2$	1,05,167	7.84

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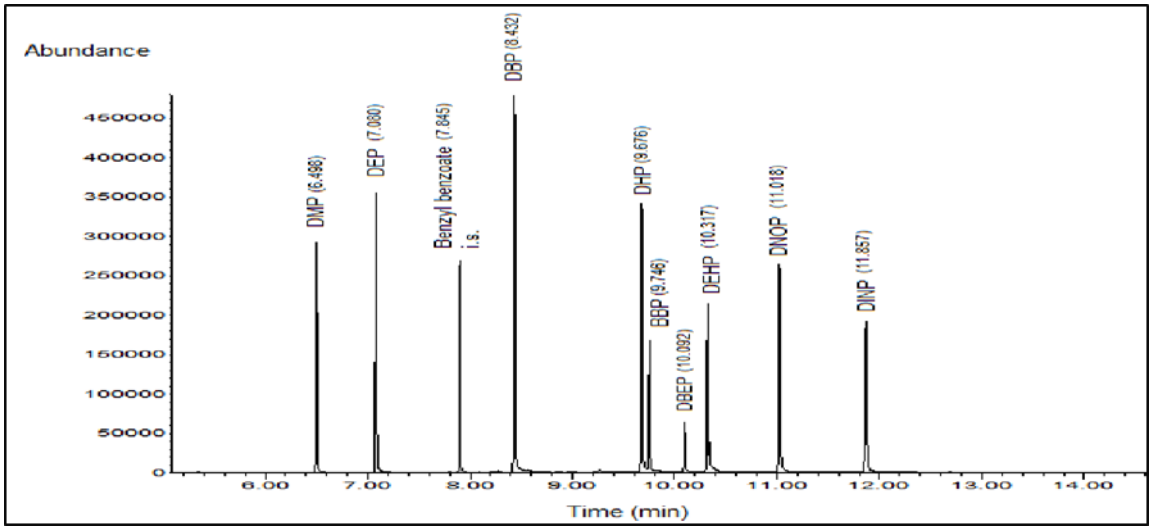

Fig.1 Chromatogram in selection ion monitoring (SIM) mode of dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), dihexyl phthalate (DHP), butyl benzyl phthalate (BBP), bis (2-n-butoxyethyl) phthalate (DBEP), bis (2-n-ethylhexyl) phthalate (DEHP), di-n-octyl phthalate (DNOP) and dinonyl phthalate (DINP).

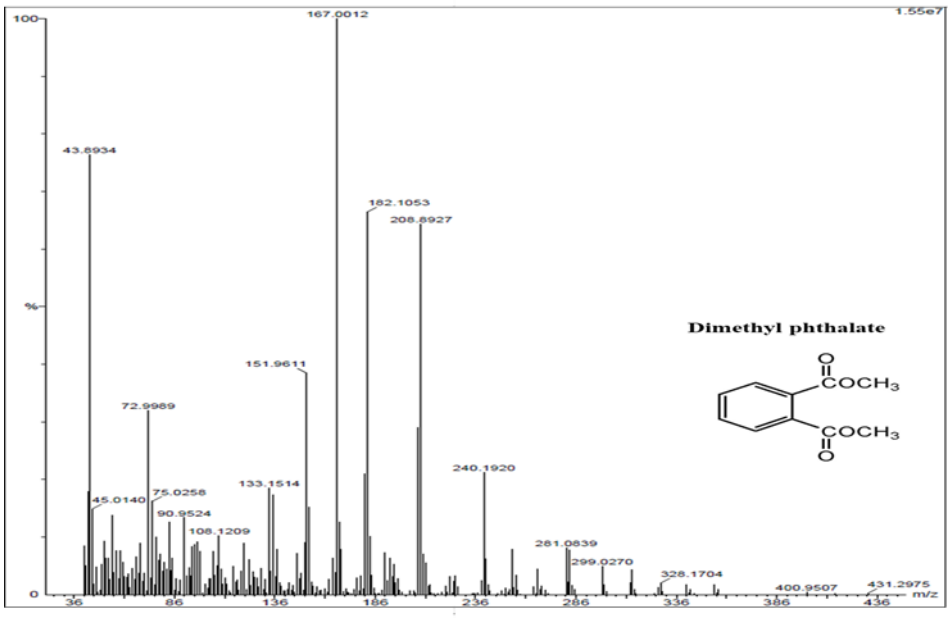

Fig. 2 GC-MS Spectra of Dimethyl phthalate

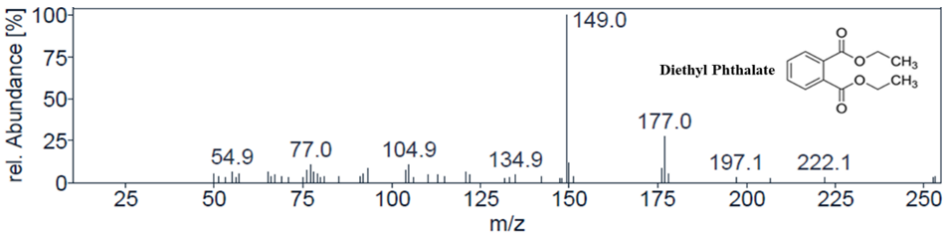

Fig.3 GC-MS Spectra of Diethyl phthalate

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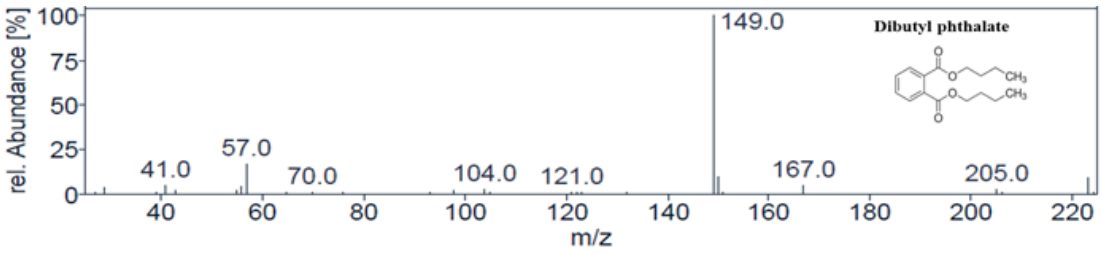

Fig. 4 GC-MS Spectra of Dibutyl phthalate

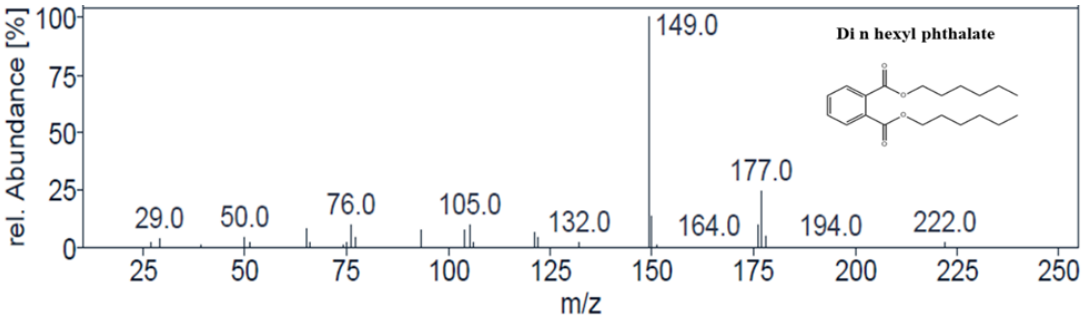

Fig.5 GC-MS Spectra of Di hexyl phthalate

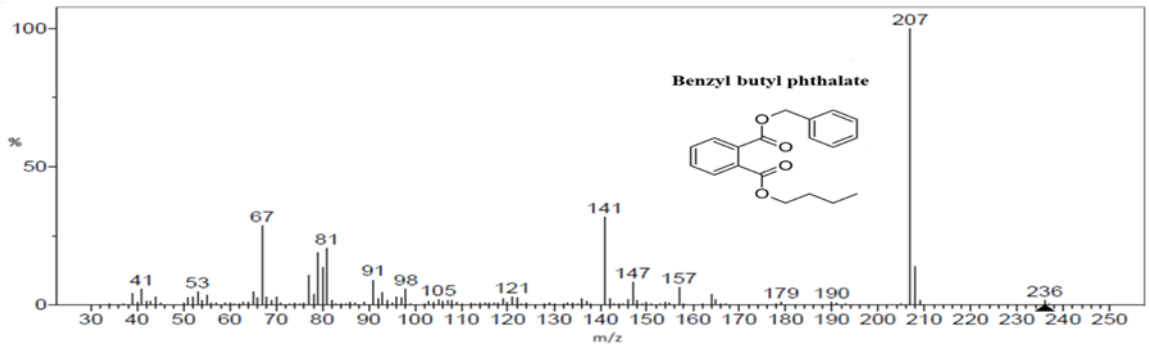

Fig.6 GC-MS Spectra of Butyl benzyl phthalate

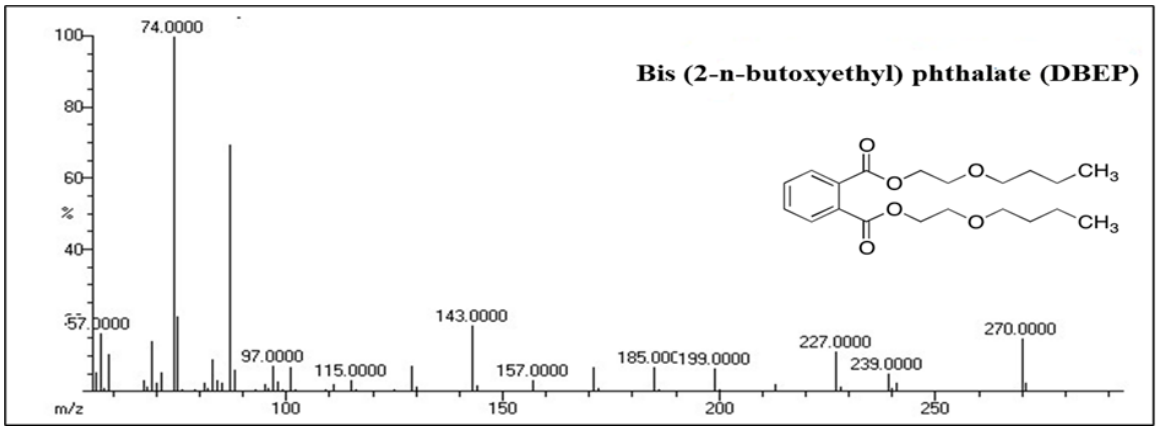

Fig. 7 GC-MS Spectra of Bis (2-n-butoxyethyl) phthalate

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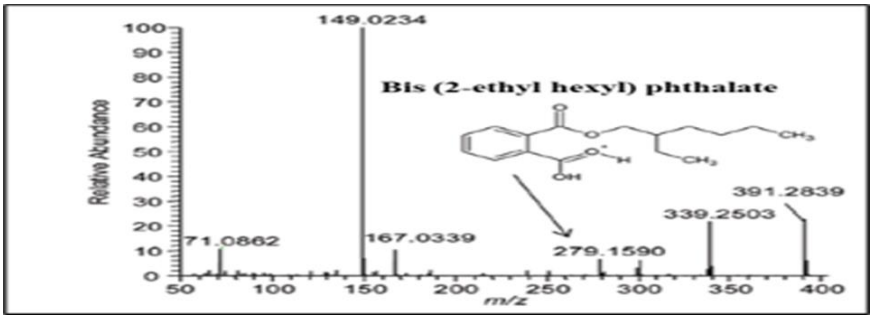

Fig.8 GC-MS Spectra of Bis (2-ethyl hexyl) phthalate

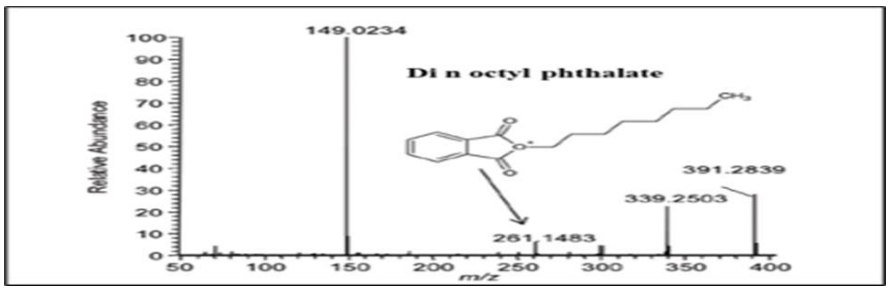

Fig.9 GC-MS Spectra of Di n octyl phthalate

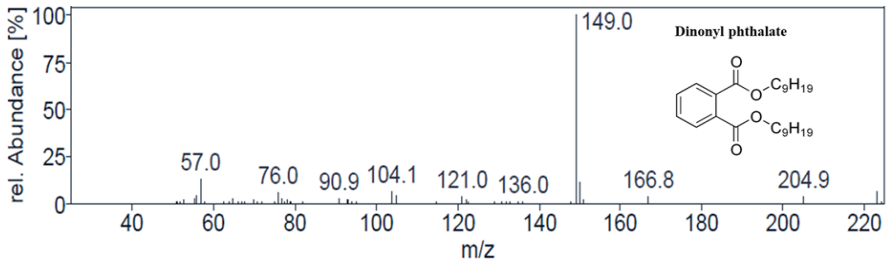

Fig. 10 GC-MS Spectra of Dinonyl phthalate

Quantification of phthalate plasticizers

Results on quantification of phthalate plasticizers in Group I and II are reported in Table 2, shows the significant differences in the concentrations of phthalate esters were observed between the group I and group II test .However, among the identified phthalates, DMP, DEP, DINP, DONP and DBP were below their quantification limit in the case of group I test sample comparable with that of control, where traces of phthalates are not detectable.

Whereas in the case of group II, all the 9 phthalates (DMP, DEP, DBP, DHP, BBP, DBEP, DEHP, DINP and DNOP) being detected, showed the highest variability in terms of concentrations. In particular, Group II test sample (33-45 yrs) showed the highest concentrations of DMP, DEP, BBP, DEHP, compared to all other phthalates ($P < 0.001$ vs each control) suggesting that the exposure to these phthalates is expected to be harmful.

Table 2 Phthalate ester concentrations in Control (20-32yrs; 34- 45 yrs), Group I (20-32 yrs) and Group II (33-45 yrs) [n=30]

Phthalate μgml^{-1}	Groups				
	Control (20-32 yrs)	**Test (20-32 yrs)**	**Control (33-45 yrs)**	**Test (33-45 yrs)**	**P value [a]**
DMP	0.04 ± 0.01	0.126 ± 0.01	1.12 ± 0.09	3.565 ±0.27	<0.0001

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DEP	0.15 ±0.22	0.29 ±0.09	1.162 ±0.25	3.64 ±0.37	<0.0001
DBP	0.11 ± 0.27	0.46 ± 0.21	0.925 ±0.14	2.72 ± 0.23	<0.0001
DHP	0.17 ±0.06	0.733 ±0.34	0.981 ±0.51	2.57 ±0.89	<0.0001
DEHP	0.11 ±0.21	0.7 ±0.61	0.98 ±0.45	3.49 ±1.24	<0.00014
DBEP	0.03 ± 0.12	0.9 ± 0.20	0.89 ± 0.64	2.15 ±1.99	<0.0001
BBP	0.21 ± 0.15	0.52 ± 0.1	0.77 ± 0.1	3.95 ± 0.35	<0.0001
DINP	ND	0.02 ±0.1	0.64 ±0.12	2.24 ±0.08	<0.0001
DONP	ND	0.03 ±0.10	1.12 ±0.22	2.9 ± 0.04	<0.0001

Note: Data are presented as mean (SD): control group; $p<0.05$ considered statistically significant between the groups.

5. DISCUSSION

Blood samples of human beings might be a better and more favourable matrix in comparison with other body fluids, viz., urine, saliva, and breast milk, to determine the exposure and circulating levels of phthalate metabolites in humans. Reports of Sakhi *et al.*[7] and Barun et al. [8] say that the use of consumer products was responsible for the presence of low molecular weight (LMW) phthalate esters like monomethyl, dimethyl, monoethyl phthalates in blood.

Gas chromatography-mass spectrometry (GC-MS) is the preferred method for phthalate identification due to the high reproducibility and specificity. Full scan acquisition and selected ion monitoring were used to simultaneously detect the phthalates and to provide sufficient sensitivity for their identification and/or confirmation. Individual phthalates were identified by comparison of their retention times (RT) and mass fragmentation patterns; the m/z range of 40–400 was selected to include the phthalate fragment ions with the highest molecular weight and to exclude fragment ions with high and low molecular weight.

Almost all the cosmetic products, including lipsticks and talcum powders, do contain phthalate esters. According to research by Parlett *et al.* [9] and Duty *et al.* [10], the personal health care products used by women might elevate the level of phthalates in their blood. This was supported by a study that investigated the relationship between the usage of personal care products and urine levels of nine phthalate metabolites by high-performance liquid chromatography-isotope dilution tandem mass spectrometry [11].

According to Serrano *et al.* [12], the diet plays a vital role for the presence of high molecular weight phthalates (HMW) in blood. These studies make us to understand that the presence of low- and high-molecular-weight phthalates in women participants could be due to the long term usage of plastic products. According to National Research Council 2008, Human exposure to plasticizers such as phthalate poses health risk for the general population.,

Ballesteros *et al.*,[13] studied that high concentrations of certain metabolites might be due to the fact that DEHP is the most used plasticizer and DBP together with DEP, BBP and DONP are quite common components in plastic bottles and also in personal care and pharmaceutical products . Both phthalates, DBP and DEHP are classified by the European Union as toxic to reproductive system and data in experimental animals are of concern for humans.

As per the study by Zamora *et al* [14], the phthalate metabolites alter sleep during the menopausal transition by altering sex hormones in women and to investigate the associations between exposure to EDCs (phthalates, phenols, and parabens) and sleep health indicators. Single spot urine samples were collected from a pilot sample of 91 women in their midlife years between 2017 and 2019 for cross-sectional studies in order to measure the urinary concentration of individual phthalates, phenols, and parabens as well as to calculate the summary concentration of phthalate combinations. A case-control study by Mukherjee Das *et al* [15] with 171 participants was carried out by GC-MS to measure the urinary quantities of six phthalate dieters. Geometric means were then computed to evaluate the relationship between phthalate exposure and breast cancer risk.

In order to maintain homeostasis in vivo, the endocrine glands release hormones, which are part of a very intricate and strictly regulated network throughout the

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body. Human health may suffer from any endocrine system abnormalities or illnesses. Since environmental endocrine-disrupting chemicals (EDCs) are so common there has been a growing interest in the relationship between EDC exposure and the prevalence of human disorders. Exposure to some environmental toxins has been found to be strongly linked to three major endocrine diseases: obesity, thyroid disease, and diabetes mellitus. There is evidence linking phthalates to the risk of endometriosis. The purpose of this meta-analysis is to assess the relationship between endometriosis and five distinct phthalate metabolites. The analysis's findings suggested a possible link between endometriosis and exposure to mono- (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) [16].

A study done by Pednekar *et al* [17] was to compare the levels of BPA and phthalates that infertile and fertile women were exposed to internally in their plasma samples. To measure BPA and four phthalate monoester metabolites at the same time, a sensitive gas chromatographic-mass spectrometric (GC-MS) technique was created. BPA was found in 29% of fertile women's plasma samples and 77% of infertile women's plasma samples viz MBzP, BPA, and MEHHP, plasma concentrations were noticeably greater in infertile women than in fertile ones.

Endocrine-disrupting substances called phthalates have also been connected to unfavorable pregnancy outcomes. There has been conflicting information regarding the effect of phthalate exposure on women's capacity to conceive and sustain pregnancy, despite the fact that female reproductive systems are sensitive to oxidation-reduction response stress and endocrine disturbance. The study by Nobles *et al.*, [18] to ascertain how exposure to preconception phthalate metabolites is related to a) fecundability and pregnancy loss and b) indicators of putative biological processes, such as oxidative stress, inflammation, and reproductive hormones.

A major contributing factor to the development of diabetes in the MASLD population is biological aging, which is defined as the progressive deterioration of physiological function over time. It raises the risk of IR and diabetes by accelerating cellular senescence and disrupting metabolic homeostasis. According to a recent study, phthalates linked to biological aging may raise disease risk, suggesting that phthalates and biological aging may have a combined influence on diabetes. However, further research is required to examine how phthalates and biological aging interact with IR, prediabetes, or diabetes. The possible link between phthalate exposure and diabetes risk has drawn a lot of attention in recent years [19]. Many epidemiologic studies have examined this connection but there have been disagreements and discrepancies over their conclusions [20-22].

Studies on humans and animals have provided evidence that exposure to phthalates may have a negative impact on the reproductive results of females. A study by Hauser *et al*., [23] assessed the relationships between the results of assisted reproductive technologies (ART) and urine levels of phthalate metabolites and found elevated levels of phthalate in urine samples.

Hence this study recommends the avoidance or minimal usage of plastic products by the human population to avoid multiple health hazards caused by them.

6. CONCLUSION

In comparing short term and long-term plastic using women volunteers, the blood samples of long term volunteers showed increased amount of DMP, DEP, BBP and DEHP metabolites. This could have been to prolong usage of plastics during their life span. Low molecular weight and high molecular weight phthalate metabolites are associated with serious health disorders like obesity, Infertility, thyroid dysfunction ,diabetic mellitus and other metabolic disorders .Previous studies have reported that usage of plastic products could lead to endometriosis, hormonal imbalance and cancer. Hence this study recommends the avoidance of usage of plastic products wherever possible and to use alternate to plastics. Phthalates containing cosmetic products should be replaced with natural and herbal products.

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