REVIEW ARTICLE

# Triphenyl Phosphate (TPHP) Exposure: A New Threat Linking Endocrine Disruption, Microbiome Dysbiosis, and Endometrial Carcinogenesis

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**ABSTRACT**

Triphenyl phosphate (TPHP), one of the widely used organophosphate flame retardants and plasticizers found in nail polish, consumer products and environmental media, becomes a potential endocrine-disrupting chemicals (EDCs) that poses risk to reproductive health and cause cancer. This review describes the desperate narrative of TPHP in disrupting hormonal homeostasis and its potential impact on endometrial cancer. Researchers observed that applying nail polish, increased the levels of DPHP, a metabolic byproduct of TPHP, by ~ 7 fold. Exposure to TPHP, has been associated with the changes in ER behavior, such as upregulation of ERα and down-regulation of ERβ in endometrial tissues in an invitro model. These alterations result in unopposed estrogenic stimulation, which in turn enables abnormal growth of endometrial cells and carcinogenesis. In addition, TPHP exposure disrupts the human microbiome in both the gut and endometrium, connecting environmental exposure to microbial dysbiosis and immune-metabolic disturbance. This review emphasizes the imperative to scrutinize more in depth the effects of TPHP exposure on estrogen signalling, microbiome stability, and their combined actions in endometrial carcinogenesis.
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**Keywords:** Triphenyl phosphate; Cosmetics, Endocrine disrupting chemicals, Estrogen receptors; Microbiome dysbiosis; Infertility, Women health

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## INTRODUCTION

The threats that endocrine-disrupting chemicals (EDCs) like pesticides, and other synthetic chemicals- pose to environmental health are gradually becoming a huge concern because of the pervasiveness of the different chemicals in our environment, food, and products we use on a daily basis. These are chemicals capable of affecting hormone production, metabolism, and action, which in turn affects the normal physiological activities and reproductive cycles. EDCs have been attributed to infertility, adverse pregnancies, and numerous malignant conditions. Children are the most sensitive as they may demonstrate greater levels of such substances due to constant hand-to-mouth action and elevated quantities of the organophosphate esters (OPEs) in baby products (1). Although researchers have conducted various studies revealing the health impacts of widely used cosmetic chemicals such as parabens, bisphenol A, glycerin and phthalates, still there is lack of awareness regarding the risks of using nail products particularly triphenyl phosphate (TPHP). Despite increased public and scientific interest, TPHP, a substance of widespread use in nail polishes, hair sprays, and other personal care products remain underreported. Even chronic exposure to low dosages is cause for concern due to its increasing prevalence, particularly among cumulative cosmetics users. TPHP has been reported to accumulate in human tissues, indicating that it requires further investigation, as confirmed by studies of biomonitoring. There is a contribution of the primary metabolite of TPHP, diphenyl phosphate (DPHP).

Based on the new findings, nail polish has the potential to be a significant source of the long-term exposure to TPHP in people who have the appropriate occupation (2). There are few researches that study the negative effects of TPHP in human population. The exposure of TPHP has been attributed to the cardiotoxic, genotoxic, metabolic, and endocrine disrupting effects in experimental studies of zebra fish, mouse, and rat (3,4). Here we literate the evidence of how endocrine disruptors affects both men and women reproductive health, the development of the breasts cancer, prostate cancer, neuroendocrine, thyroid, metabolism and

weight problems and cardiovascular endocrinology. Various research studies using the next-generation sequencing method suggest that the microbiome dysbiosis represents a potential etiological variable in the incidence of several gynaecological disorders, which includes endometriosis, chronic endometritis, irregular menstrual bleeding, endometrial cancer, and infertility (8).

The scope of study in this review is to critically evaluate the evidence linking triphenyl phosphate exposure to endocrine disruption, microbiome dysbiosis, and their combined contribution to endometrial carcinogenesis.

## ENDOCRINE DISRUPTORS

Endocrine-disrupting chemicals (EDCs) are exogenous substances or a mixtures that interfere with any aspect of a hormone's function (Fig.1). Several exogenous chemicals are commonly added to products, including flame retardants, food additives, medications, personal care products, and insecticides (9). Exposure to EDCs has been linked to such consequences as irregular menstruation, impaired fertility, and pregnancy problems in women (10).

### Classes of EDCs

The most familiar type are synthetic estrogens (e.g., diethylstilbestrol), phytoestrogens (e.g., isoflavonoids), pesticides (e.g. organophosphates) (Kumar and Tsimi, 2023), and industrial chemicals (dioxins, flame retardants). The compounds enter the body through ingestion, breathing or the placenta, and also the developmental phase is most susceptible to their impacts (11, 12).

### TPHP and its sources

Organophosphate ester (OPE) is a type of flame-retardants and plasticizer used globally, and its consumption has increased after the banning of polybrominated diphenyl ethers. (13). It is usually present in food wrappings, cosmetics, and it is identified in the environment in forms like water (14) and air (15). Triphenyl phosphate (TPHP) is an organophosphate compound, and widely used chemical formula is P(C6H5)3. It consists of three phenyl rings (C6H5) which are relayed on a core of phosphorus. In crystals they are colorless and very hydrophobic, are more ecologically risky to the soil environment when compared to other OPEs.

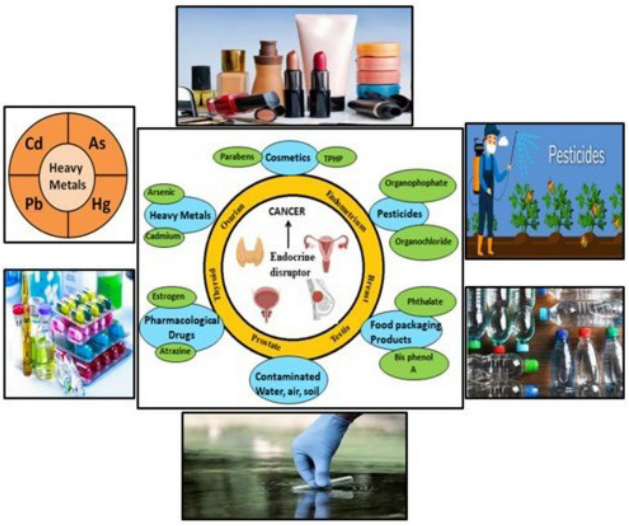


**Figure 1: Sources of Endocrine disruptor**

It has been detected across multiple environmental compartments, including indoor dust, atmospheric particulate matter, river water, groundwater, drinking water, soil, sediments, and wastewater (14). The concentrations of TPHP released by wastewater treatment plants have been estimated to be up to 3500 ng/L, this source is recognized as the major source of discharge into water bodies and a significant contributor to aquatic pollution. In addition to the environmental matrices, TPHP has been detected in biological matrixes. It has been found in pollutions of aqueous and terrestrial life, as well as in human urine, blood, chorionic villi (placenta tissue), placental tissues and breast milk (15,16). Special concern has been raised about its toxic effect during the embryonic development, since zebrafish studies indicated alterations in protein expression and metabolic dysfunction upon exposure. In humans, TPHP is metabolised into diphenyl phosphate (DPHP), hydroxylation of TPHP (OH-TPHP) and dihydroxy-TPHP ($(OH)_2$-TPHP) occur (17). The presence and bioactivity of both TPHP and its metabolites create a potential risk to human health and the environment. Recent evidence also indicates that TPHP may be a disruptor of the human microbiome (Table 1) and as such could impact health.

### Route for TPHP exposure

People are often exposed to TPHP through three pathways: oral, inhalation and percutaneous. Derma exposure in particular has gained attention as a predominant route, particularly for consumer products like nail polish and flame retarded objects. This pathway is especially relevant since it circumvents the protective checkpoints of the body and facilitates a direct absorption of TPHP through the skin (18). Previous studies have also demonstrated that dermal contact could be the major exposure route of TPHP in those situations. For instance, in a study urinary biomarkers of TPHP were still substantially lower even when participants painted their nails using gloves. However, skin applications in absence of gloves result in a significant elevation of these biomarkers, proving the function of skin contact as facilitating agent for absorption (19).

Inhalation is also a significant route, especially indoors, where TPHP has been identified in airborne particles, dust and electronic or treated furniture emissions. Inhalation of airborne TPHP particles may cause respiratory exposure, as part of systemic absorption and toxicity

(20). Ingestion, often through hand-to-mouth contact or contaminated food and dust, leads to accumulation of TPHP in digestive organs, where it is metabolized into its primary metabolite, diphenyl phosphate (DPHP), and distributed to multiple tissues including the lungs, testes, liver, brain, and heart (21).

The skin, being the largest organ and major interface with the environment, is especially vulnerable to chemical exposures in industrial settings, workplaces, and daily product consumers (22). TPHP absorption through the skin depends on several factors such as the chemical's concentration, duration of exposure, skin condition, and the presence of enhancers like solvents or alcohol. Being lipid-soluble, TPHP can readily pass through the stratum corneum of the epidermis, enter systemic circulation, and exert potential endocrine-disrupting and toxic effects (23).

Few human data are available on TPHP toxicity, however pertinent toxicological research has suggested that it may cause endocrine disruption, an adverse effect on reproductive rights and unknown development, and genotoxicity related health issues. The article by (24) has also mentioned that the median concentrations of DPHP were approximately two times higher among women than men, implying the differences in the exposure patterns regarding the respective sex.

TPHP use in nail polishes are most likely underreported, as it was detected in unlabelled products, indicating incomplete ingredient disclosure (6). Researchers observed that applying nail polish boosted the levels of DPHP, a metabolic byproduct of TPHP, by ~ 7 fold within 10 to 14 hours. TPHP is not a safe substitute, as it has been shown to exhibit endocrine-disrupting properties. Women appear to bear a disproportionate burden of TPHP exposure, as evidenced by studies showing approximately double the levels of its metabolite DPHP compared to men (24).

**Mechanism of EDC**

EDCs are hazardous chemicals that which interfere with the hormonal balance in the body by acting as mimics or antagonists of natural hormones such as estrogen, thyroid hormones, and testosterone. EDCs structurally resemble endogenous hormones (25), binding to estrogen receptors (ERα and ERβ), which interfere with gene expression an evidenced by an invitro model (55). Figure 2 shows how EDCs mimic or block endogenous estrogen (E2) and its binding to receptors. This dysregulated receptor signalling may cause an overgrowth of the endometrial cells, disrupted apoptosis, and development of cancer (26). The EDC-recptor complexes transit to nucleus, and hinder the regular transcriptional control mediated by estrogen. This leads to aberrant gene and mRNA expression, especially genes associated to puberty and reproduction. Furthermore, EDCs creating changes in the epigenetic processes, including the DNA methylation

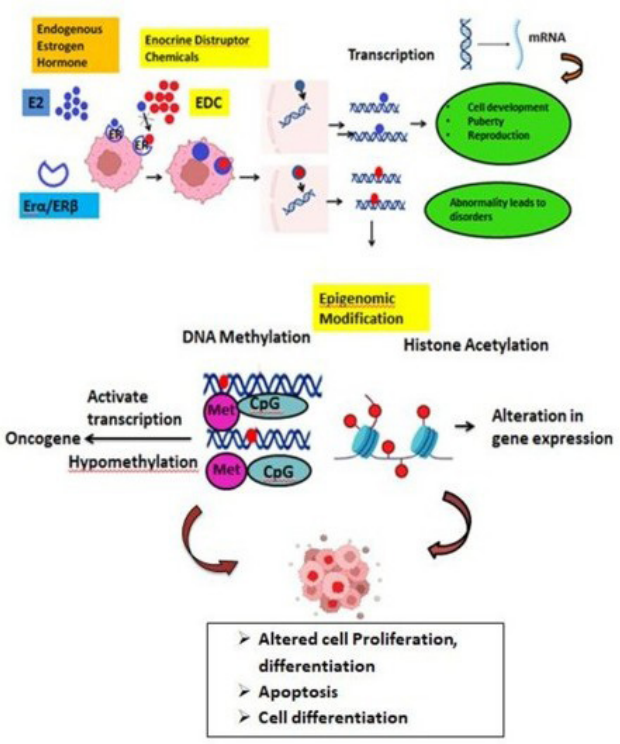


**Figure 2: Mechanism of EDC**

and histone acetylation, which further enhances the unusual cell growth and immune evasion. One of the most widespread EDCs, triphenyl phosphate distorts the process of lipid metabolism by altering methylation of metabolic gene (e.g., ACACA, PLIN2, CRLS1) in both zebrafish and human liver cells (27) and can result in inappropriate stimulation of oncogenes. According to the study, the main targets of TPHP and its metabolite, diphenyl phosphate (DPHP), were the crucial signalling proteins, such as SRC, MAPK1/3, HSP90AA1, and IGF1R, which control the cell proliferation, differentiation, and survival (28, 29).

Furthermore, EDCs can alter nuclear receptors (NR) such as estrogen receptor (ER), androgen receptor (AR), aryl hydrocarbon receptor (AhR), etc., to disturpt the synthesis, degradation, transcription of hormones in vivo, leading to hormonal disorders (30). When AhR, a ligand-activated transcription factor, modulates the expression of genes upon its interaction with EDCs, potentially resulting in transgenerational epigenetic effects (31, 32). Over the past 50 years, exposure to EDCs has been related to a rise in reproductive disorders including but not limited to early puberty, infertility, hormone-sensitive cancers and developmental disorders (33, 34).

## ENDOMETRIAL CANCER EPIDEMIOLOGY AND ETIOLOGY

EDC's are highly linked to the endometrial cancer due to the hormone interference, namely "Estrogen". Endometrial cancer is the 6th common gynecologic

cancers and the most common types of uterine cancer. Endometrial cancer does not have established screening programs nowadays, even though the cases and mortality rates of uterine cancers are surging over the last several decades (35). Most of the risk factors associated with endometrial cancer also explain the higher prevalence of endometrial cancer in developed nations and these include obesity, ageing populations, insulin resistance, high levels of exogenous estrogen and sedentary life styles (36). Recent research on the endometrial microbiome suggest that the evaluation of the microbial environment may be key to improving our understanding of endometrial proliferation, embryo apposition/attachment/invasion, and establishment of early pregnancy (37). The study of the microbiome is typified by great discoveries and technicaldevelopments, and stands at the dawn of a new beginning, and could have a revolutionary impact on the awareness of human health and disease (38). It is claimed that up to 15 percent of cancer contribute to the advancement of the microorganisms. Recent evidence suggests that unique bacterial densities and compositions are associated with various stages of endometrial neoplasia, thus making the microbiome a potential therapeutic target and predictive factor of endometrial cancer.

## ENDOMETRIAL MICROBIOME

Microbiome is one of the main factors in determining the etiology and methodology for preventing the prevalence of endometrial cancer since it is associated to the amount of estrogens in the estrogen-related carcinomas (39). It is possible to state that the diversity and composition of endometrial microbiota is one of the aspects of great significance to the immunopathogenesis of endometrial cancer. So far very little research has been conducted regarding the structure of the microbiota in the endometrium and this is an aspect that needs further long term research to ascertain the vitality of the microorganisms in maintaining symbiosis and the development that leads to dysbiosis (40).

In the recent past, the uterus of a healthy woman was regarded to be sterile environment. However, over the past decade, the existing body of studies began to outline the microbiome of the higher female reproductive tract and study its possible connections to health and illness (41). On the one hand, the active human endometrium is rather important plays a crucial role in maternal and embryonic development. Any impairment of the endometrium can lead to the occurrence of pregnancy loss and endometrial cancer. The female reproductive system can harbor bacteria that affect the occurrence of endometrial malignancies that develop due to such etiological adjustments such as DNA mutability, the formation of vasculatures, dissemination of the epithelial lining, chronic inflammation, and physiological imbalance (42).

The most likely microorganisms that involved in endometrial health are bacterial genus variations, while the Lactobacillus genus has been most consistently described as prevailing and healthy in a healthy endometrium. Some of the other common commensal genera reported in endometrial microbiota of healthy women include *Acinetobacter, Bacillus, Barnesiella, Bifidobacterium, Blautia, Corynebacterium, Enterobacter, Escherichia, Fusobacterium, Gardnerella, Jonquetella, Parabacteroides, Prevotella, Propionibacterium, Pseudomonas, Ralstonia, Shigella, Staphylococcus*, and *Streptococcus* (43). The researchers conducted studies that established dissimilar endometrial microbiota signatures with absence of Lactobacillus dominance. In a study (44), 16S rRNA sequencing of hysterectomy samples was used to study 25 women with fibroids or hyperplasia, and the authors reported a colonization of the uterus by *Acinetobacter, Pseudomonas, Comamonadaceae*, and *Cloacibacterium* (16).

### Linking Endometrial Microbiome to Cancer

Recently, evidence suggests that the aberration of endometrial microbiome lies at the forefront of endometrial cancer (45). There are complicated effects to the structure and composition of the human microbiome because of accidental or chronic exposure to endocrine-disrupting chemicals (EDCs) that are available in consumer products. Such changes can alter the local immunological responses, facilitate inflammation, and adversely modify protective effects of beneficial microorganisms. A healthy endometrium is inhabited by predominant Lactobacillus species and the environment is controlled tightly to maintain a balanced, protective microbial environment. Nevertheless, microbial dysbiosis, including a reduction in Lactobacillus and the overpopulation of potentially pathogenic genera, such as Anaerococcus, Porphyromonas, Shigella, and Barnesiella, has been linked to inflammatory syndrome, abnormally occurring uterine bleeding, and endometritis, all of which are the risk factors of endometrial cancers (8, 46, 47). As noted by the International Agency for Research on Cancer (IARC), the incidence of cancer and death due to cancer, such as endometrial cancer, will increase exponentially by 2040, and therefore, it is important to determine the role of microbiome imbalances in the development and progression of the disease.

### TPHP toxicity

Although human data on the toxicity of triphenyl phosphate (TPHP) is scarce, an emerging research environment has demonstrated the multifactorial and potentially problematic nature of endocrine interactions between species (48). There has been very high concentrations of TPHP and its dominant metabolite, diphenyl phosphate (DPHP), have been detected and are prevalent in human tissues all over the planet, with more than 60 percent of the breast milk samples sampled in Japan, the Philippines and Vietnam (49).

TPHP may disrupt sex steroid hormone balance in a human adrenocortical carcinoma cell line (H295R) by interfering with their synthesis, metabolism, or receptor-mediated activation (50). (51) demonstrated that a 5-day exposure to TPHP inhibited population growth and altered metabolites in two freshwater green algae species.

Recent researchers discovered that triphenyl phosphate (TPHP) presents severe dangers to reproduction of aquatic life by means of complex endocrine-disruption, and effects increase during a similar proportion as the approach the exposure. After a 100 days of exposure to realistic environmental TPHP levels (0.131 to 1.773 µg/l), Japanese medaka (Oryzias latipes) stated that there was a delayed ovarian development and the production of eggs significantly reduced by 38.9-50.9 % (52). This inhibited the production of a key estrogenic signal, the vitellogenin (vtg). Acute exposure (14 days; 196 g/L) activities in parallel with zebrafish (Danio rerio) resulted an increase in plasma concentrations of 17β-estradiol and testosterone, suggesting that tested chemicals interfered with steroidogenic pathways (53). These data highlights that TPHP has the capacity to act relatively intricately in interference with hormones whereby there is more than one possible course of action that has to be critically assessed of the risk of organophosphate flame retardants in aquatic ecosystems. A study by (54) found that TPHP exposure in zebrafish significantly disrupted levels of histamine and γ-aminobutyric acid (GABA) neurotransmitters and decreased total acetylcholinesterase (AChE) activity, a known biomarker for neurotoxicity.

TPHP has been demonstrated to exhibit bioconcentration behavior depending on the life forms. Further analyses will imply that the presentation of TPHP can lead to developing toxicity in water lifeforms including zebrafish embryos, which interfere with profile clear articulation of proteins and their metabolic processes. According to (55) isolate exposures to TDCIPP and TPHP to zebrafish caused a reduction in fertility evident through reduced hatching and endurance. Malignant growth of endometrial and endocrine disruptor can activate cell cycle development and reproduction. It is based on such revelations that the observation and analysis of the ecological and organic impact of TPHP is emphasized to easily comprehend its role in biosphere and human wellbeing environment. (56). In Gobiocypris rarus, the quantity of cranial nerve cells and the dendritic process of pyramidal cells were significantly impacted by the outcome of TPHP. As a result, the fish had poor memory and learning (57).

**TPHP-Mediated Hormonal Dysregulation**

TPHP is being researched on an increasing basis for its possible involvement in hormone-related malignancies, such as endometrial cancer. Despite not being formally recognized as a direct cause of endometrial cancer, new research indicates that TPHP may influence the development of endometrial cancer by interfering with hormones (58).

As many studies accumulate expression of the toxicity of TPHP, shedding light on how it will affect development and metabolism, especially that of aquatic organisms, knowledge on how it will affect human health is still murky, especially with reproductive cancer (59). Considering the knowledge about endocrine-disruption of organophosphates, and hormone-sensitivity of endometrial cancer, there is reasonable assumption that chronic exposure to TPHP can be used in promoting carcinogenesis by disrupting hormone, immunity, or microbiota.

**Glucose Metabolism Disruption by TPHP**

By examining the influence of TPHP on pubertal mice, (60) found that the exposure of pubertal females to TPHP repressed the process of glucose glycolysis and activated gluconeogenesis. The effects of TPHP are similar in a male rat diabetes model with UCD-T2DM (61), where the author found that prenatal exposure to TPHP raised the frequency of the development of type 2 diabetes.

**Endocrine Disruption and Pubertal Timing**

The correlation between endocrine-disrupting chemicals and onset timing of puberty has aroused a lot of attention that appears to be multifaceted and complicated (62). (63) stated that exposure to TPHP cause an arrest in the cell cycle at the G1/S shift, apoptosis, and a substantial reduction in colorectal cell viability. According to histological examination, TPHP damaged the cellular structure. of the colorectal tissue. Other TPHP effects include altered thyroid hormone levels, reproductive toxicity (e.g., decreased semen quality), altered metabolic function leading to weight gain, developmental toxicity, and genotoxicity (DNA damage).

**TPHP and Endometrial Carcinogenesis Pathways**

(64) demonstrated that exposure to triphenyl phosphate (TPHP) triggers the ERβ/NF-κB signalling pathway, promoting cell proliferation and cell cycle progression in Human Ishikawa endometrial cancer cells. Previous studies have shown that TPHP to can enhance transcriptional activity of many nuclear receptors including ERα.TPHP is an endocrine disruptor, which has an adverse effect on the function of thyroid (65). In women of childbearing age, there is a reproductive hormonal imbalance. (66) observed that decreased expression of ZO-1 and occluding, important tight junction proteins, in mouse ileal and colonic epithelium following TPHP exposure leads to the inflammation bowel disorder, cancer, neurodegenerative, and neuroinflammatory disease. There has also been a complaint that exposure to TPHP causes reproductive toxicity such as reduction in male fertility and a reduction in sperm quality (67). It has been reported that both male and female rats

have an impaired pubertal development, and that TPHP can penetrate the blood brain barrier in mice, raising concerns of neurotoxicity (68). Animals studies have further clarified the link between endometriosis and EDCs. High doses of ethinyl estradiol (EE) given orally to pregnant mice between days 11 and 17 of pregnancy increased the incidence of endometriosis lesions in the offspring (69).

There is an emerging body of information indicating that TPHP has the potential to disrupt human microbiome significantly. Prenatal exposure to TPHP impaired intestinal microbial homeostasis (dysbiosis) and interfered with the production of biliary acids and short chain fatty acids in the animal model, predetermining an offspring with obesity, fatty liver, and insulin resistance in adulthood (70). Furthermore, aquatic models implies that the alterations of the microbial community caused by TPHP may influence the microbiota phenotype by interacting with the microbiota, the gut and the brain (71). In the face of an ever-increasing level of knowledge of microbiome interactions with the host, an increasing number of questions are being raised as to whether anthropogenic pollutants of our environment such as TPHP play some role in destabilizing the microbial ecology, thereby compromising microbial activity and host responses (immune or metabolic). The development of this kind of insight is essential in determining the health hazards of these chemicals. It is not established yet how concentrated TPHP can be found in nail polish, to what extent it is exposed to humans after applying, and whether it might induce endometrial cancer. On reviewing about the endocrine disruptor, TPHP (organophosphate) chemical plays a major role in cancer development. Endometrioid carcinoma in grades 1 or 2 is frequently associated with dysregulation of estrogen, particularly in cases of hyperestrogenism (72).

**Estrogen Stimulation and Endometrial Cell Proliferation**

TPHP has been recognized as a potential ostrogenic endocrine disruptor. Repeated exposure to TPHP can potentially resemble the actions of unopposed estrogen in terms of regulation of estrogen receptors in the absence of progesterone (73). Such hormonal imbalance may result in constant stimulation of the uterine surface, promoting excessive cell proliferation. TPHP. like endogenous estrogen, has also been demonstrated to activate estrogen receptor-mediated signalling, such as the PI3K - AKT - GSK-3beta -cyclin D1 -pRB - cascade, which helps to increase progression through the cell cycle and prevents the initiation of apoptosis (74). When these effects are not counteracted by adequate progesterone signalling to endometrial cells, these are exposed to continued mitogenic stimuli. This may increase the threat of abnormal cell division, the buildup of genetic changes, and eventually malignant transformation, implicating TPHP as a probable factor in the endometrial carcinogenesis based on disruption of estrogenic processes (75).

**Identification of EDC in Human**

Differential and genome-wide association analyses in diverse human biological samples are necessary to identify endocrine-disrupting chemicals (EDCs) (HBM, GWAS). These approaches are complimentary in that they identify the EDCs, evaluate genome susceptibility in light of exposure, and aid interpretation of molecular perturbations caused by exposure (Fig. 3).

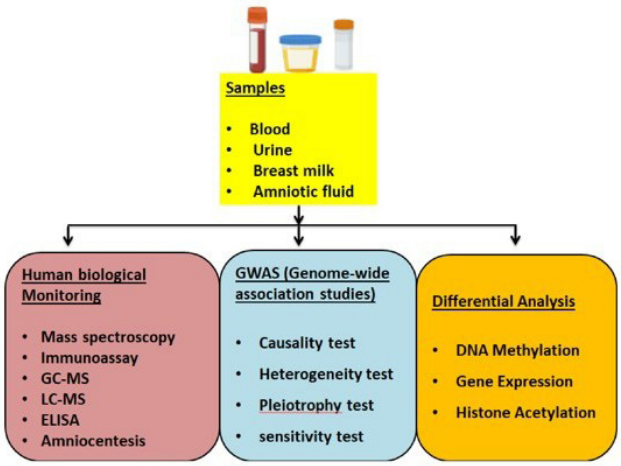


**Figure 3: Identification of EDC in human**

## CONCLUSION

This emerging evidence emphasizes the complex interplay among environmental toxicants, TPHP is a biologically active contaminant than benign chemicals that potentially play a role in modulating the pathogenesis of EC. Although TPHP and DPHP was not previously regarded as a significant threat to health, they are recently detected in human biological samples.In addition, the expanding facts increasingly highlight its ability to interfere with hormonal signaling pathways, activate estrogen receptor alpha (ERα), and disturb microbiota homeostasis all together augmenting endometrial cancer promoting potential.

Research in aquatic and rodent models has shown that TPHP triggers estrogenic effects, cell damage, metabolic perturbation, and hormone disruption. Its metabolite diphenyl phosphate (DPHP) has been detected repeatedly in studies of urine, breast milk and placental tissues from humans, indicating considerable exposure with potential adverse health impacts. The question is particularly important for women exposed to TPHP-formulated cosmetics, chiefly nail polish, when dermal absorption becomes a major route.

Current evidence suggested that TPHP disrupts these bacterial communities, further establishing an association between chemical exposure and immunological, metabolic and inflammatory factors that contribute to the development of cancer. TPHP has its ability to act as an estrogen analogue, disrupt hormonal equilibrium, affect gene expression and perturb human microbiota

suggests its contribution in development of hormone dependent cancers like endometrial cancer. This review suggests that TPHP exposure, primarily from cosmetics such as nail polish, may be implicated in cancer progress through a variety of routes: direct activation of ERα, imbalance of hormones, and dysbiosis with microorganisms. While existing data is predominantly preclinical or observational, it demonstrates sufficiently worrying signs with respect to chronic exposure and indicates that further toxicological and epidemiological research is also required in humans.

Future research should prioritise well-designed epidemiological studies that assess the links between chronic TPHP exposure and hormone-dependent malignancies in humans. Integrated mechanistic research incorporating toxicological, endocrinology, microbiome science, and omics techniques are required to unravel causative pathways. Real-world exposure scenarios, such as cosmetic use, vulnerable populations, and the cumulative effects of chemical mixes, deserve special study. Such study will be critical for improving risk assessment, guiding regulatory choices, and establishing preventative efforts to reduce the possible health consequences of TPHP exposure.

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