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REVIEW ARTICLE

Environmental Contamination and Chronic Exposure to Endocrine-Disrupting Phthalates: An Overlooked and Emerging Determinant for Hormone-Sensitive Cancers

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Abstract | Despite several modifiable and non-modifiable risk factors of hormone-associated cancers have been established, less heed has been paid to chemicals, those having the potential to thwart the body's normal detox system and affect the endocrine-hormonal pathways. Phthalates are endocrine-disrupting chemicals, most widely manufactured and used indiscriminately in several industries, including processed, ultra-processed and packaged food, single-use plastics, household and personal care/cosmetic products including diapers and electronics. The general population is regularly being exposed to phthalates on contact with these products, especially women and children are most vulnerable. It is therefore highly crucial to monitor and evaluate the biological burden of plasticizing phthalates in humans and understand the potential mechanisms of etiological link between pervasive exposure to phthalates and development of chronic diseases such as cancer through epigenetic and/or genetic alterations. It is also important to identify sustainable and scalable interventions for increasing public awareness, and restricting chronic phthalate exposure to individual and the population at large through relevant policy legislations, particularly in low-income and middle-income countries, such as India.

Keywords: *Phthalates, Endocrine-disrupting chemicals, Everywhere chemicals, Hormone-associated cancers, Epidemiology, Processed food, Food packaging, Public health, India*

1 Introduction

It was only over the last two to three decades that various hormone-mimicking industrially-made chemicals that accumulate in the environment have set the focus on *endocrine-disrupting chemicals* (*EDCs*). These are categorized as agents that mimic and perturb the normal hormonal activity responsible for regulating our body's basic physiological functions like cellular differentiation, tissue and organ development, reproduction and behavior[1, 2]. The unregulated contamination of our environment as a consequence of indiscriminate use of these industrially-made chemicals poses a grave concern to the ecosystem, wildlife and public health. Moreover, due to evident inter- and intra-trans-generational epigenetic inheritance, the effects of EDCs are not restricted to the exposed generation[3, 4]. The endocrine system is a coordinated crosstalk between different tissues and organ sites interacting through several hormones, mediating specific signals for desired action. It has been suggested that environmental

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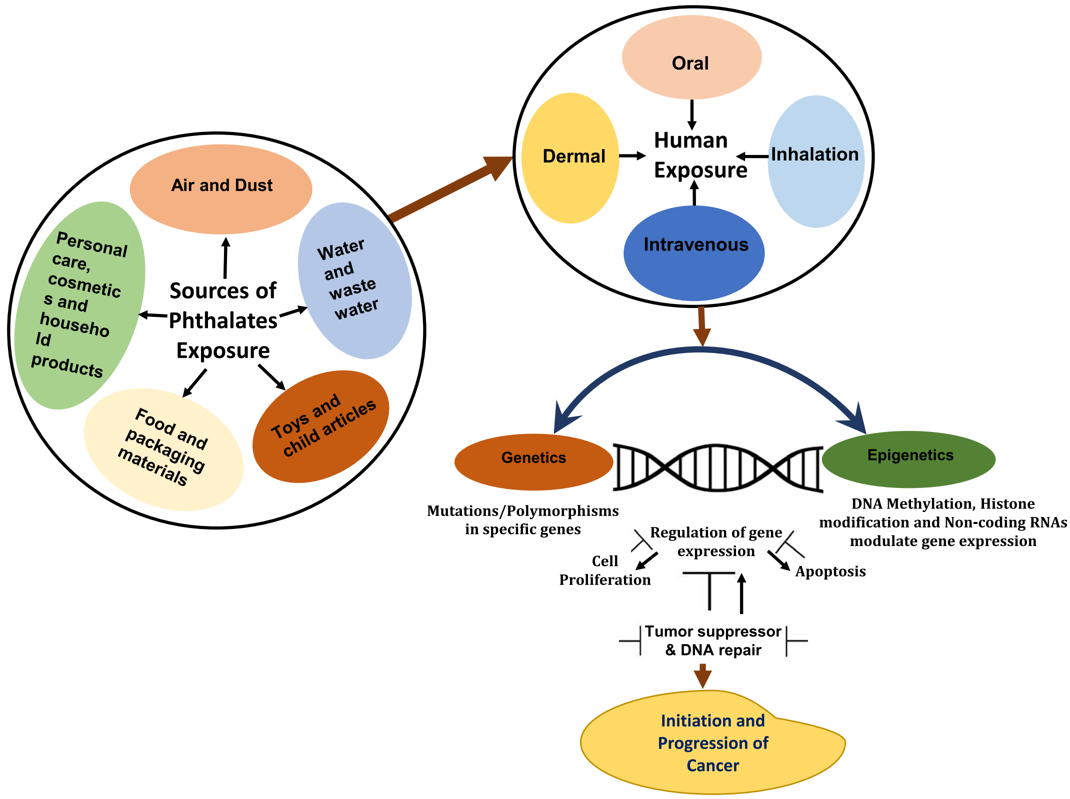

Figure 1: The model provides an overview of the different environmental sources from which phthalate concentration levels have been estimated having implications for public health. Human exposure to phthalates can occur through various routes including ingestion, inhalation, dermal and intravenous. Sustained chronic exposures could play a crucial role in the clinico-pathology and prognosis of hormone-sensitive cancers through its interactions with the genetic as well as epigenetic mechanisms of the body. Upon exposure to endocrine disrupting phthalates, the tumor suppressor genes and the DNA repair system simultaneously work towards reducing cellular damage. Alterations due to epigenetic modifications and/or mutations/polymorphisms in the key genes due to persistent everyday exposure to phthalates can cause improper functioning affecting gene expression, and cancer initiation and progression.

chemicals, such as phthalates, could be interacting with the hormonal system, thereby aberrantly modulating their action in an agonistic/antagonistic manner[5]. They are capable of activating and/or repressing several signaling pathways, thereby disrupting endocrine systems, leading to initiation and progression of various chronic diseases, including hormone-dependent cancers (see Fig. 1).

Recent reports have shown an increasing trend of hormone-dependent cancers world over[6]. Despite identification of key modifiable causal factors and advancement in diagnostics and treatment strategies for cancer management, the burden appears to be surging each year with tumor recurrence, treatment resistance, metastasis and deaths presenting a major challenge. It is possible that sustained pervasive exposure to specific EDCs could play a statutory role in manifestation of the above challenges affecting risk of cancer development and poor clinical prognosis. EDCs are estimated to cost the USA, $340 billion and the EU, € 163 billion as annual healthcare costs and lost productivity[7–9] along with a similar cost attributable to phthalate-specific disease burden and mortality[10, 11]. Therefore, the significant threat posed by EDCs, including *plasticizers* to public health and the society at large, cannot be ignored and underestimated.

2 Phthalates as Plasticizing *EDCs*: An Overview

Plasticizers are chemicals added to plastic products to increase their flexibility and durability. There are over 500 different plasticizers among which the utmost focus remains on phthalates, which are most widely manufactured, marketed and used in polyvinyl chloride (PVC) plastics and flooring, in making child products including toys and diapers, processed food and packaging, single-use plastics, paints, pharmaceuticals, medical devices, catheters, blood transfusion devices, personal-care products and cosmetics. These are also added as fragrance enhancers and clouding agents in the food processing industry, and also utilized in packaging/cardboard materials[12–15]. Dietary exposure is one of the most important routes of contact to phthalates, but significant exposure is also possible via air, drinking water and skin through contact with household products, cosmetics, electronic materials and clothing.

Globally, over 3 million tons of phthalates are consumed with an estimated market of 10 billion USD in 2020[16, 17]. The USA alone produces and imports more than 213,000 tons of phthalates each year as estimated by the US EPA (Unites States Environmental Protection Agency)[18]. Europe produces approximately a million ton of phthalates each year. Also, among the most commonly used phthalates, DBP (di-butyl phthalate), DEHP (di-2-ethyl-hexyl phthalate) and DINP (diisononyl phthalate) are used most frequently (about 75%) with an expected burden of 6.76 million tons in 2019[19, 20]. This escalated production of phthalates caters to the higher demand for plasticized products giving an opportunity to the plastic industry to make its way into multiple newer industries churning out lighter and cost-effective articles. Furthermore, recent evidence of human, wildlife and marine contamination with micro-plastics and microbeads, deliberately added to several consumer, personal-care products and processed food has incrementally contributed to the existing massive problem of chemical pollution[21]. The possibility of phthalates leaching out of these plasticized consumer products has been extensively studied and debated with their carcinogenic, mutagenic and genotoxic implications to population health[22–26]. Phthalates have been detected in human urine, serum, breast milk, placenta and tissue samples[27–30]. They are not just highly estrogenic, but also act through, and mimic other hormones affecting the nuclear and steroid receptors, and have been shown to cause developmental toxicity with potential public health implications[3, 24]. Moreover, despite efforts by the USA[31], EU (European Union)[32, 33] and Japan[34] to curb use of such chemicals in selected items, such as toys and personal care products, they are still exploited, more predominantly in low-income and middle-income countries, such as India, due to their easy availability, usefulness in multiple industries and lack of suitable and safe alternatives along with lagging public awareness, and homogenous nation-wide and global policy regulations[35].

3 Extent of Phthalate Contamination in India

3.1 In Air and Dust

Studies have explored the seasonal variations pertaining to concentrations of phthalic acid esters (PAEs) in Delhi and found significantly higher concentrations of phthalates during winters with an average concentration of 703.1 ± 36.2 ng/m^3[36]. Li et al.[37] reported that phthalate concentrations in New Delhi, India (884 ± 474 ng/m^3), were 2.3 times higher than those in Xi'an, China (268 ± 98 ng/m^3). In Raipur, India, Giri[38] analyzed aerosol samples and found that concentrations varied between 2 and 926 ng/m^3 with higher concentrations in winter. In contrast, Fu and colleagues also found higher concentrations of phthalates in Chennai, especially during summer[39]. Similar observations were made by Sampath et al.[40] who recorded a highest total phthalate during summer (52 ng/m^3) and pre-monsoon (61 ng/m^3) season and found that urban areas represented the highest concentration of 836 ng/m^3. Other studies analyzing ambient aerosol particles have also shown higher concentration of phthalates during the summers than in winters[41, 42]. It is possible that an increased vaporization of phthalates from plastic/PVC, packaging and electronic waste materials due to extreme hot temperature during the summers could be a factor for the presence of higher concentration of phthalates in air and dust. It is also interesting to note that the phthalate concentrations showed wide seasonal and geographical variations along with difference between urban and rural settings. This in-turn indicates that human exposure to phthalates and its metabolites is variable to a great extent and depends on the place of residence, the individual and community practices along with the climatic influences. Moreover, community practices such as increased coal and crop residue burning, which are common practices in India, may contribute to higher level of phthalate exposure. Further, the fertilizers and insecticides containing plasticizer formulations used in the agricultural fields for pest control are also burnt along with the residual crops resulting in increased public health concern from chronic exposure to phthalates.

3.2 In Water and Sediment

Studies examining phthalate contaminations in water samples including drinking water from Mysore city, South India, have reported the presence of Di-butyl-phthalate (DBP) with concentrations in range of 46.79–212.52 μg/L[43], exceeding the recommended upper limits of 0.6 μg/L and 0.8 μg/L set by US EPA (Environmental Protection Agency) and WHO, respectively[19, 44]. Other studies have quantified phthalate concentrations from wastewater and found contamination of several phthalate diesters[45–47]. Gani et al.[48] reported the presence of DEP (diethyl phthalate), DBP, BBP (benzylbutyl phthalate) and DEHP in the untreated wastewater in North India, with DEHP having highest mean concentration of 28.4 ± 5.3 μg/L. Measurement of wastewater is a unique method to identity consumption patterns of various substances such as pharmaceutical chemicals, pesticides, food and packaging materials including single-use plastic within communities. Successful elimination of chemical compounds such as phthalates from wastewater is crucial as the reclaimed water may be released into the major water bodies, particularly in developing countries like India, with subsequent contamination of aquatic life. This may have serious public health consequences, because of exposure through food chain consumption of aquatic animals such as fishes and molasses including vegetables grown using the reclaimed contaminated water. Phthalate esters are detectable in water and soil sediment samples from Gomti River in North India[49], Kaveri River in South India[50] and from surface riverine sediments of Ganga River[51]. These studies show that di-2-ethyl-hexyl phthalate (DEHP), di-butyl phthalate (DBP) and di-ethyl phthalate (DEP) were predominantly detected in all the samples. Studies by Khalid in Periyar River, South India[52], have also shown significant evidence of phthalate contamination. The reason for elevated concentration of phthalates in water and sediment samples estimated from several Indian rivers could be a consequence of the dumping pattern of plastic, electronic scrap, personal care and industrial waste.

3.3 In Food, Packing Materials and Children's Toys

Migration of phthalates from packaged goods has been evaluated, particularly from bottled water and milk packets, showing that the total phthalates in bottled water and milk were in the range of 39–7820 ng/L and 56–686 ng/g, respectively, with higher mean phthalate concentrations in packaged milk[53]. Food packaging materials such as Sambar (food spice most commonly used in South India) packets made up of polyethylene were also analyzed showing DEHP leachates in 20% of the samples[54]. Das et al. conducted a study among urban Delhi population and found that DEHP was the most abundant phthalate with an estimated daily intake of up to 70 μg /kg/day. They categorically found that food remained the major source of exposure[55]. The presence of high concentration of phthalate leachates in variety of most essential regularly used food packets such as water, milk, oil, spices is highly alarming and requires risk estimation and urgent policy decisions to ban plastic packaging. The specific migration limit (SML) of phthalates in food has been set by the European Commission with a regulation, stating that concentrations greater than 0.3 mg/kg for DBP, 1.5 mg/kg for DEHP and 30.0 mg/kg for BBP should not be allowed to be used and marketed[56]. The European Commission has also recommended that DEHP, BBP, DBP, DIBP should not be used because of their evidently strong toxic effects on human health, particularly in toys and child care products having concentrations greater than 0.1%, which should not be marketed[57]. However, in the absence of policy regulations regarding endocrine-disrupting chemical biomarkers like phthalates in India, a study showed that majority of the toys available in the Indian market have traces of one or more phthalates, including DEHP (96%), Di-iso-nonyl phthalate (DINP) and di-iso-decyl phthalate (DIDP) (42%) at concentrations ranging from 0.1 to 16.2%[58]. This indicates that children in India are highly exposed to phthalates and its metabolites from childhood making them highly vulnerable, presenting a huge public health concern. The chronic early life or childhood exposure to phthalates could alter the body's hormonal homeostasis, altering the hypothalamus–pituitary–thyroid axis along with causing genetic and epigenetic modulations, leading to development of early onset health issues, such as reproductive disorders including early puberty, growth and developmental issues and other related health problems.

3.4 In Human Urine/Serum/Plasma

Investigations categorically focusing on measuring the concentrations of phthalates and its metabolites in biological samples from the Indian subcontinent are scarce. However, the burden of phthalates in India is no less than that of the other countries with data showing that out of seven Asian countries, urinary concentrations of phthalates in India are 398 µg/mL, which is much higher than those of China (234 µg/mL), Vietnam (133 µg/mL), Japan (120 µg/mL), Korea (117 µg/mL) and Malaysia (95 µg/mL). The predominant phthalates found were mono-ethyl, mono-methyl, mono-2-butyl, mono-n-butyl phthalate and several metabolites of DEHP[59]. A report from Tamil Nadu, India, revealed the presence of phthalate di-esters in urine samples collected from the general population. DMP (dimethyl phthalate), DEP, DBP and DEHP were most frequently detected with mean concentrations in the range of 36.3 ± 30.3 ng/mL, 19.8 ± 12.6/ng/mL, 49.3 ± 36.2 ng/mL, 47.1 ± 26.6 ng/mL, respectively[60]. They have also reported that phthalate concentrations are higher among women and children than in men, probably due to increased use of cosmetics, toys and other personal care products. Phthalates estimation from serum samples of patients with infertility issues and endometriosis has also been done[61, 62]. Our study on estimation of phthalates from pre-treatment urine samples obtained from invasive breast cancer patients shows that phthalate di-esters namely di-butyl phthalate (DBP) (100%), di-2-ethylhexyl phthalate (DEHP) (98.75%), di-ethyl phthalate (DEP) (98.75%), di-methyl phthalate (DMP) (11.25%), benzyl-butyl phthalate (BBP) (11.25%) and di-n-octyl phthalate (DInOP) (26.25%) were detected in higher concentration range of 2.27–2,069,698 ng/mL, ND-4330 ng/mL, ND-152.14 ng/mL, ND-35.45 ng/mL, ND-55.02 ng/mL, and ND-8896 ng/mL, respectively. Significantly higher phthalate concentrations were observed for women having triple negative breast cancer phenotype[63].

3.5 Cancer Concerns Linked to Phthalates Exposure

The rising incidence of hormone-dependent cancers[6] such as of the breast, ovary, endometrial, thyroid, prostate and testes reflects concerns for the possibility of clinico-pathological role of industrially-made ubiquitous environmental chemicals, such as phthalates in initiation, progression as well as clinical prognosis of cancer. Current evidence from laboratory studies shows that exposure to phthalates can lead to increased cell proliferation and growth, cancer migration, invasion and treatment resistance through modulation of gene expression along with activation and/or repression of several proteins and signaling cascades[64–80]. This has been further corroborated by studies which conclusively demonstrate that phthalates can not only cause aberrations in early mammary gland development and modulate the genomic profile of the mammary glands but also can promote epithelial to mesenchymal transition and sensitize cancer stem cells leading to treatment resistance, metastasis and cancer recurrence[81–90].

Epidemiologic studies have well characterized the effects of plasticizers in the development of reproductive health disorders[91], while other studies on phthalates exposure and increased risk of cancer indicate that phthalates are associated with prostate[92], thyroid neoplasm[93, 94], breast[95–100] and endometrial carcinoma[101]. They are also found to be associated with uterine fibroids and leiomyomata[102, 103]. However, these studies associating phthalate exposure to cancer pathogenesis are insufficient and have mostly been conducted in the western population with conflicting results. However, there exists a substantial dearth of similar studies from low- and middle-income countries (LMICs) such as India.

The idea that human exposure to low concentrations of phthalates is safe is controversial with evidence contradicting these claims[104]. BBP, DBP and DEHP are the three most commonly studied phthalates, where exposure to low concentrations of these chemicals has shown to mimic the actions of steroid hormones through molecular mimicry with possible tumor inducing and metastatic behavior[70, 79]. In silico studies have shown overlays of phthalates at the natural binding sites of steroid hormone receptors (estrogen/progesterone/androgen receptors), reflecting that phthalates mimic binding patterns of natural ligands and categorically bind in a similar fashion to the active binding sites. The critical windows of susceptibility such as during prenatal, perinatal, infancy and early childhood are most pertinent due to vulnerability of chemical exposure having implications in cancer development later in life, also having inter-generational and trans-generational consequences through alterations in both genetic and epigenetic imprints[3, 4]. Furthermore, due to the archaic nature of tests and experiments used by the accredited agencies and industries to measure the safety of these chemicals, the methods are not appropriate for endocrine-disrupting chemicals, such as phthalates, primarily because low or very low concentration testing is not done, though phthalates significantly perturb the balance of the food chain at various trophic levels to disrupt the hypothalamus–pituitary–thyroid signaling axis[106, 107].

3.6 Strategy for Research and Prevention

The current evidence suggests extensive environmental contamination of phthalates in air, aerosol and dust particles, drinking and river water, food and packaging materials, cosmetics, waste water, including body fluids like urine, with significantly higher concentrations in majority of the sampling mediums in India, indicating an immense public health concern. However, estimation of phthalates in crops, vegetables and aquatic animals such as fishes has not yet been done, which seems to be of importance for providing safe agricultural and aquatic food materials. The growing burden of phthalates in the environment is primarily due to increased marketing and use of variety of plastic/PVC-based articles along with indiscriminate utilization of cosmetics and personal care/beauty products. Burning of coal, staple and other waste materials, emissions from vehicular exhaust are all rich sources of phthalate contamination. Studies have also indicated toward seasonal, geographical and site-specific variations in the concentrations of different phthalates, the possible reasons for which include increased hydrolysis and vaporization of plastic/PVC materials due to high temperature and burning of residual crops with fertilizers and pesticides.

The ever-increasing burden of hormone-dependent cancers and evidence from human and laboratory studies indicates that plasticizers, such as phthalates, have the potential to modulate the susceptibility to hormone-associated cancers. However, more high-quality omics-based data are required to elucidate the extent to which these compounds cause genetic and/or epigenetic alterations, leading to carcinogenic transformation. It is very clear that endocrine disruptors such as plasticizing phthalates present a major global public health challenge that needs to be given a higher research priority, particularly in developing countries, so as to curb exploitation of these compounds and prevent further environment and human exposure, ultimately contributing to alleviating burden of phthalate-associated early onset cancer among young adults.

Molecular and genomic epidemiological studies that take into consideration the individual genetics, family history and geographical susceptibility patterns among individuals and specific communities are required in providing relevant etiological insights for effective assessment of human exposure to phthalates with a consequent risk of developing cancer along with identification of genetic/epigenetic abnormalities following chronic exposure to phthalates. Global analysis of genomic, transcriptomic, and whole genome and epigenome studies could provide valuable insights into the spectrum of abnormalities between normal and cancerous tissues upon chronic exposure to plasticizers. Moreover, to fill in the lacunae on the existing environmental burden and exposure patterns of phthalates, it is essential to initiate programmes, similar to the ones implemented in the USA[108], Canada[109] and the European Union[110, 111], for region-wise bio-burden estimation of environmental phthalates, especially in LMICs including India, so as to estimate the environmental contamination and human exposure levels that are responsible for cancer initiating effects of these compounds.

Restricting inclusion of phthalates through relevant behavioral interventions and in making polyvinyl chloride plastics and other consumer/personal/childcare products through effective policy initiatives along with identifying relevant safe alternatives can help in limiting the higher production of phthalates, subsequently reducing its toxic exposure, and effects on human and wildlife. Overall, the rapidly increasing demand for plastic products is inadvertently creating a huge havoc to the environment, human and animal life and it needs to be controlled urgently through relevant policy regulations.

Publisher's Note

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Author contributions

AMD conceived and designed the review, collected data, drafted and edited the manuscript. AG, RJ, RBR and BCD contributed to the design, critical review and adding relevant scientific content to the manuscript. All authors read, revised and approved the final manuscript.

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Declarations

Conflict of interest
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