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REVIEW ARTICLE

Di-2-Ethylhexyl Phthalate (DEHP) Toxicity: Organ-Specific Impacts and Human-Relevant Findings in Animal Models & Humans - Review

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Abstract

Di-2-ethylhexyl phthalate (DEHP) is considered one of the most extensively used plasticizers in polyvinyl chloride (PVC) products that include medical devices, food packaging and flooring materials. However, DEHP has been classified as an endocrine disruptor and there is a global concern regarding its effects on human and animal health. The current review seeks to summarize the existing body of literature on the toxicology of DEHP in relation to a wide variety of organ systems, including endocrine dysfunction, testicular, ovarian, renal, neurotoxic, hepatotoxic, and cardiotoxic *in vivo* and *in vitro* effects performed on animal models and humans. The review will also address the potential DEHP-replacement measures in order to limit global DEHP use and ensure a safer environment. The use of DEHP and its derivatives has a particularly serious impact on the health of the reproductive system along with the development processes due to their ability to externalize influencing hormones. Several studies on both animal models and population samples have shown that DEHP exposure has adverse reproductive effects, organ abnormalities, and chronic health issues. This review aims to investigate DEHP exposure-related reproductive toxicology, mechanisms by which toxicity occurs, and prospects for finding less hazardous substitutes (Graphical Abstract).

Keywords

Di-2-ethylhexyl phthalate, Endocrine disruption, Testicular toxicity, Ovarian toxicity, Endometriosis, Renal toxicity, Neurotoxicity, Hepatotoxicity, Cardiotoxicity, Reproductive toxicity, Environmental health

Introduction

Di-2-ethylhexyl phthalate (DEHP) is a common additive used in commercial products and is classified together with other plasticizers [1]. This substance is frequently added to polyvinyl chloride (PVC) materials to enhance their flexibility as well as development resilience [2]. DEHP is present in the blood tubes and bags, medical and dialysis apparatus, toys, containers of soft drinks, food products, and building materials [3]. However it is worth emphasizing that DEHP plastic is an analogue for use regarding conventional consumer goods but because of its leachability into ecological systems and tissues of human organs the health risks associated are gradually increasing mining due to its largely use and also noticeable endocrine disrupter activity [4].

Molecular Structure

Molecular structure: Di-2-ethylhexyl phthalate (DEHP) is a member of the phthalate family and is an organic ester molecule. A phthalate backbone [benzene-1,2-dicarboxylate] esterified with two 2-ethylhexyl groups (C_8H_{17}) makes up its molecular structure [1].

Chemical Formula: $C_{24}H_{38}O_4$

IUPAC Name: Bis (2-ethylhexyl) benzene-1,2-dicarboxylate

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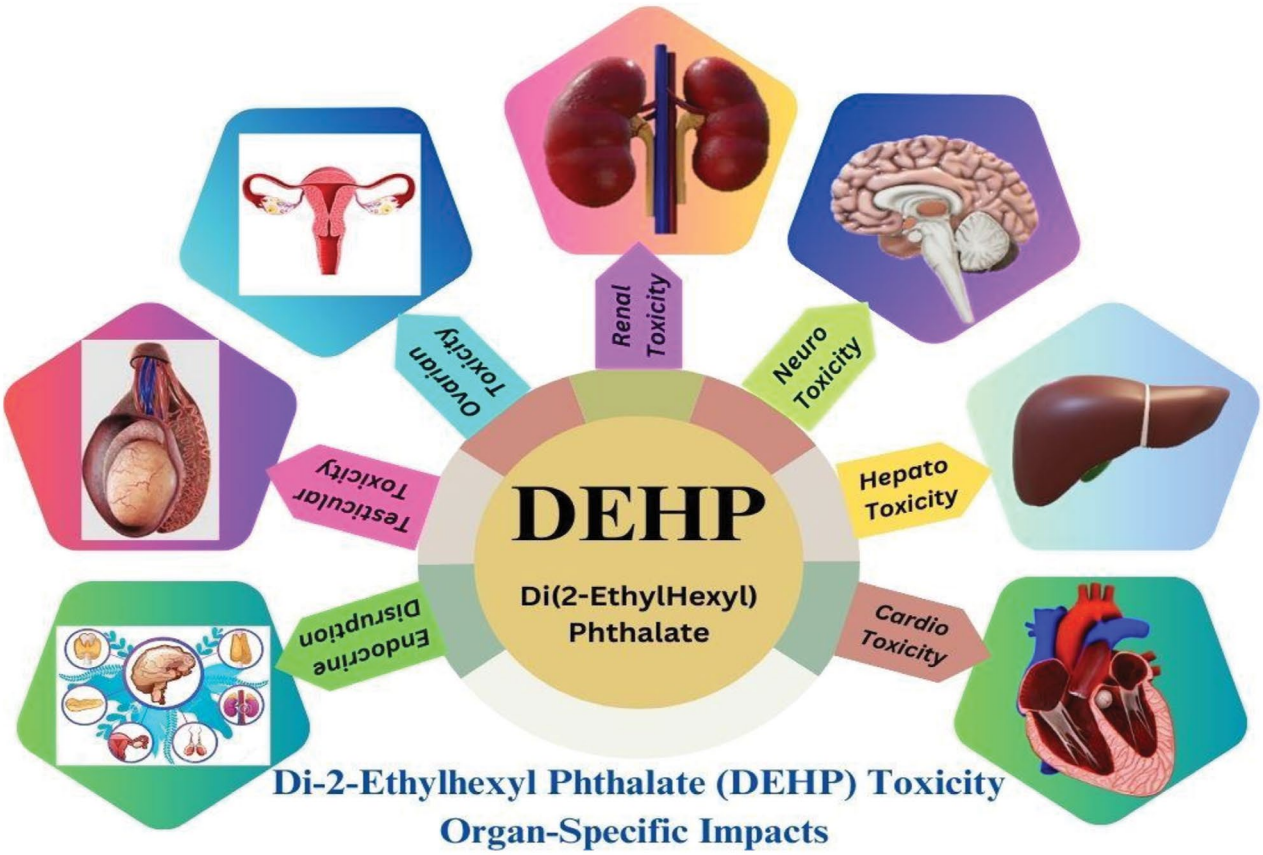
Graphical Abstract



Common Names: Di(2-ethylhexyl) phthalate, **DEHP**

Chemical Class: Phthalate Ester

Details of the structure

A benzene ring with two carboxyl groups (-COOH) at positions 1 and 2 of the aromatic ring makes up the phthalate backbone [benzene-1,2-dicarboxylate].

The carboxyl groups are esterified to the two 2-ethylhexyl groups. Each 2-ethylhexyl group is made up of an octyl chain (C_8H_{17}) with an ethyl group ($-CH_2CH_3$) joined to the second carbon of a six-carbon backbone on one of the carbons. The crucial component of DEHP is the ester bond that forms between the phthalate and the 2-ethylhexyl groups.

Molecular weight

Molecular Weight of DEHP: 390.58 grams per mole (g/mol). This value is the total of the mass of all the chemical elements that make up the structure of the molecule namely carbon, hydrogen, and oxygen. DEHP in contrast with many solvents or gases has a relatively larger molecular weight which has a part in its biological system because the molecule is not readily excreted outside.

The active form of DEHP is Mono-2-ethylhexyl phthalate (MEHP), which is also said to produce some of DEHP's harmful effects. The risk of health defects seems to be higher for sensitive populations such as foetus, infants, and those who make use of DEHP-containing medical instruments or work in an environment that has DEHP. Exposure of populations to DEHP has been correlated with several harmful conditions including, adverse reproductive health, risk of endocrine system disorders and impaired development of the nervous system.

The aim of this review is to integrate information available in animal models as well as human studies to arrive at a better comprehension of the toxicological aspects of DEHP. Furthermore, we seek to investigate alternative plasticizers which could be utilized for industrial purposes to lessen DEHP-related health risks.

Dosage in toxicology studies

Dose, time, and route of exposure are key determinants of the toxicological effects of DEHP. The authors of various epidemiological surveys and *in vitro*, *in vivo* investigations have differed in their usage for DEHP due to the objectives of the research being conducted [5] (Table 1).

Here's the summary of the dose levels commonly utilized in toxicology studies and details their importance:

Table 1: Summary of dosage for toxicity studies.

Study Type	Route of Exposure	Typical Dosage	Effects Observed
Acute Toxicity [Rodents]	Oral or Injection	500 mg/kg to 2000 mg/kg	Lethal dose, sub-lethal effects, acute liver and kidney damage
Chronic Toxicity [Rodents]	Oral [Daily]	50 mg/kg to 500 mg/kg/day	Endocrine disruption, testicular and ovarian toxicity, liver damage
Developmental/Reproductive	Oral [Prenatal]	10 mg/kg to 500 mg/kg/day	Testicular atrophy, impaired sperm quality, reduced fertility
Endocrine Disruption	Oral or *In Vitro* [Cell Culture]	10-100 mg/kg/day [oral] Or 1 µM to 100 µM [cell culture]	Decreased testosterone, altered oestrogen levels, thyroid disruption
Neurotoxicity	Oral or Injection	50-500 mg/kg/day	Altered brain morphology, cognitive impairments in offspring
Cardio toxicity	Oral or Injection	100 mg/kg to 500 mg/kg/day	Heart damage, hypertension, altered heart rate variability

A. *In Vivo* Animal models (Rodents)

Acute toxicity:

Single dose administration:

- Oral administration: In rats and mice, single dose ranges between 500 mg/kg to 2000 mg/kg of body weight are commonly used in conducting acute toxicity studies. These doses help assess immediate lethal or sub-lethal effects.
- Intraperitoneal injection: DEHP, in some studies, is given via injection to study systemic effects. Doses in this format go from 50 mg/kg to 1000 mg/kg.

B. Chronic/Treatment for 30 to 90 days:

Daily dosing for 30 to 90 days:

- The range of typical chronic toxicity does for rodents is 50 to 500 mg/kg/day depending on goals of the study.
- For example, Gray, et al., (2000) studied effects of DEHP on rats for 28 days at a dose of 100 mg/kg/day and were able to identify decreases in testosterone levels and spermatogenesis.

C. Developmental and reproductive toxicity:

Concentrations of DEHP that could have developmental and reproductive health effects are often administered in doses that are lower and characteristic of human dosages such as:

- 10-100 mg/kg/day is used for prenatal exposure.
- Mylchreest, et al., (2000) reported that when pregnant rats were administered 50-500 mg/kg/day doses of DEHP during gestation, the testes of male offspring sustained damage.
- Jiang, et al., (2005) evaluated the effects on testicles and reproduction in male rats using 100 mg/kg/day.

D. Studies on endocrine disruption:

Low-dose, prolonged exposure is the main focus of endocrine disruption research in order to replicate doses that are relevant to the environment. Li, et al., (2009), for example, observed ovarian disruption in rats using dosages of 50-100 mg/kg/day, whereas other research evaluate endocrine changes in non-human primates using doses of 10-50 mg/kg/day.

In Vitro Studies [Cell Cultures]

Human cell lines

Because human tissues can achieve DEHP concentrations in the micromolar (µM) to millimolar [µM] range after environmental exposure, these values are commonly used in *in vitro* studies. Common concentrations range from 1 µM to 100 µM for research on human hepatocytes, Sertoli cells, or Leydig cells that focus on hormone synthesis and cell survival. For example, 2 µM DEHP was utilized in experiments investigating testosterone production in human Leydig cells, and at this dose, testosterone synthesis was significantly reduced [6].

Primary cells

In certain advanced studies, human organoids or primary liver, gonadal, or neuronal cells may be exposed to DEHP at doses ranging from 0.1 µM to 100 µM in order to simulate low-level, prolonged ambient exposures [7].

Human Exposure Studies [Epidemiology]

Typical human exposure

Exposure, to DEHP in the environment is often assessed through biomarkers like urine metabolites such as mono-2-ethylhexyl phthalate (MEHP). These metabolites serve as markers of body load. Are commonly measured in urine concentrations ranging from nanograms to micrograms, per litre. Levels of DEHP metabolites in the population can vary between 10 to

300 ng/mL due, to a person's work related interactions with the substance. These levels have been linked to impacts on the endocrine system and reductions, in sperm quality as other health effects [8].

Low-dose occupational and environmental exposure

When assessing the safety of phthalates such as Di-2-ethylhexyl phthalate (DEHP) organizations like the European Food Safety Authority (EFSA) and other regulatory bodies have established 0.05 mg/kg body weight per day as the daily intake (ADI). However real-world exposure levels frequently surpass these limits. This is especially true for individuals residing in regions with a density of PVC based products, like equipment or working in industries associated with plastics [9].

Toxicological Effects of DEHP

Endocrine disruption

Endocrine disrupting chemicals like DEHP can mimic as well as obstruct the natural hormones of the body causing an imbalance in the natural hormone cycle which can further lead to irreversible functional and developmental damage [10].

Mechanisms of action

DEHP or its metabolite MEHP are reported to act as either agonists or antagonists to important hormones receptors, namely oestrogen receptors (ER) and androgen receptors (AR) and peroxisome proliferator-activated receptors (PPAR) leading to changes in the gene expression, and epigenetic regulation that impacts the synthesis, metabolism, and action of testosterone, oestradiol, and thyroid hormones among others [11].

Endocrine Effects in animal models

It even demonstrated diminished production of testicular testosterone, Leydig cell hormone production dysregulation, and reduced sperm formation to occur among male rodents.

In females, DEHP appears to have an impact on ovarian reserve, causes follicular atresia, formation of cysts, and in some cases early menopause. It induces abnormal oestrogen cycles leading to infertility in females [12].

Human exposure and epidemiology

DEHP can be introduced to the body through food items and from certain medical equipment. Studies within populations have shown how MEHP which is present in urine was altered in men and women that had certain testosterone and oestrogen levels. Prenatal exposure to DEHP has been linked to altered thyroid hormone levels in both mothers and infants [13].

Testicular toxicity

Testicular toxicity is one of the most pervasive effects with respect to DEHP exposure and associated mechanisms. Aside from interfering with the development of testes, spermatogenesis, DEHP exposure has been shown to affect fertility and testicular health specifically [14].

Animal models: In rodent models, specifically, in rats, exposure to DEHP, is known to cause testicular atrophy as well as damage Leydig cells and testosterone levels. The chemical is responsible for sperm count decrease and decreased sperm motility. Histological studies show changes like degeneration of seminiferous tubules and loss of germ cells and Sertoli cell damage.

Studies have also shown that germ cells are affected by MEHP causing fragmentation of DNA and apoptosis which increases chances of infertility in males [15].

Humans: Studies of humans have shown that DEHP exposure by way of occupational exposure (for instance the PVC manufacturing industry) is associated with lower semen quality including decreased sperm count, defects, motility. Other studies found a relationship between phthalate metabolism and sperm DNA damage indicating that DEHP can be detrimental to male fecundity [16].

Ovarian toxicity and endometriosis

The toxicity of DEHP is not only limited to the testicular tissues as it is quite apparent that the ovaries and endometrial tissues of females are also affected by this compound [17].

Animals: Cyst formation, reduction in the number of follicles, and puberty being delayed have been observed following DEHP exposure in females, specifically rodents. Offspring of such rodents experience instability in oestrous cycles, and oestrogenic and gonadotropic function leading to premature ovarian failure and decreased fecundity later in life [18].

Endometriosis: DEHP exposure is considered a predisposing factor for women to develop endometriosis, which is characterized by the growth of endometrial tissue outside the uterus. It has been noted that MEHP is capable of activating oestrogen receptors on endometrial cells which leads to enhanced ectopic growth and endometriotic inflammation [19].

Humans: Research has indicated a causal relationship between exposure to phthalates and endometriosis in women. DEHP and some other phthalates interfere with the normal hormonal and immune functions which promote the formation of endometrial lesions and propagation of the disease [20].

Nephrotoxicity

The DEHP also causes nephrotoxicity. DEHP increases the intensity of oxidative stress and inflammation activities that contribute to renal damage [21].

Animal studies: Studies on rats indicated that chronic

exposure to DEHP leads to glomerular damage, necrosis of tubules, renal fibrosis, and impaired functions. Gross pathological changes incorporate enlarged kidneys, atrophied tubules, and interstitial inflammation.

The proximal tubules of the kidney are the most sensitive to DEHP-induced injury, and exposure will lead to low GFR, increased levels of serum creatinine, and changed protein excretion profiles in urine [22].

Human studies: Studies in humans regarding phthalates exposure have shown altered markers of renal function, especially in people with long-term exposure to DEHP in medical devices, dialysis machines, and occupational exposure. In humans, DEHP exposure is associated with an increased risk of chronic kidney disease (CKD), as presented by elevated creatinine and biomarkers of renal damage in urine [23].

Neurotoxicity

DEHP is neurotoxic as well; however, exposure especially in the developmental stages enhances neurotoxicity.

Mechanisms of Neurotoxicity: DEHP and MEHP can disrupt the central nervous system, especially as it concerns dopaminergic, serotonergic and GABAergic units primarily responsible for cognitive function, behaviour, and motor control. Exposure may lead to neuroinflammation, neurodegeneration, and synaptic plasticity disruption [24].

Animal models: Rodent models indicate that prenatal DEHP exposure results in cognition impairment, learning disability, and memory loss. These effects are most pronounced when brought on during the critical window for brain development: late gestation and early postnatal life.

MEHP has been implicated by animal models to be involved with over-apoptosis of neurons and glia activation. There is disruption of circuitry involved in emotional regulation [15].

Humans: Some epidemiological studies pointed to the development of neurotoxicity in children exposed to DEHP early in life through low IQs, attention deficit, and behavioural disorders; hence, the concerned exposure of DEHP is prenatal and early childhood exposure [25].

Hepatotoxicity

DEHP exposure results in several alterations in the liver, mainly in lipid metabolism and oxidative status [26].

Animal models: In rodent models, long term DEHP exposure leads to hepatic steatosis, necrosis of hepatocytes, and fibrosis. On histopathological aspects, it appears with the rise in lipid accumulation, increased vacuolization of hepatocytes, and inflamed liver tissues. The metabolites of DEHP, like MEHP, result in mitochondrial dysfunction and increased formation of ROS molecules that have damaging action on the liver cells and hence contribute to cirrhosis.

Long-term exposure can also exhibit potential carcinogenic effects. There is research-based evidence pointing toward the connection of DEHP exposure with the risk of tumorigenesis in the liver [27].

Human beings: Human studies regarding the use of medical devices (blood bags, intravenous tubing, etc) have revealed that chronic exposure to DEHP elevates the level of liver enzymes and affects the functions of the liver, more noticeably in infants and children exposed to products contaminated with DEHP [28].

Cardiotoxicity

The cardiovascular system is another critical target of DEHP-induced toxicity, and the effects are manifested mainly on heart function and vascular integrity [29].

Animal models: Exposure from DEHP-induced has been demonstrated in causing cardiac arrhythmias, high blood pressure, and structural changes in rat and mice hearts, including myocardial fibrosis and cardiac hypertrophy. MEHP impairs calcium signalling in the cardiomyocytes, causing muscle contraction failure and impairment of the cardiac function.

Endothelial dysfunction and increased vascular resistance have also been documented in DEHP-treated animals that resulted in hypertension and loss of vascular elasticity [30].

Humans: Epidemiological studies show that an increased exposure of DEHP, as well as other phthalates, increases the risk of hypertension, tachycardia, and overall increased risk to cardiovascular diseases among adults. Increased risk to myocardial infarction and arrhythmia was also determined among individuals with DEHP exposure [31].

Safer Alternatives for DEHP

Considering the toxicological issues related to DEHP, various industrial and medical uses demand safer substitutes. Such substitutes are as follows:

1. **Diisononyl Phthalate (DINP):** Based on the structural similarities to DEHP, DINP might be expected to have a lower toxicological profile; however it does exhibit endocrine function and reproductive disruption at doses above the levels of concern [32].
2. **Dioctyl Terephthalate (DOTP):** It is a non-phthalate plasticizer. Its toxicity is almost nil along with excellent environment compatibility. It is also gaining popularity in medical equipment as well as toys for kids due to its non-toxic characteristics [33].
3. **Citrate Esters (e.g., TEC, ATBC):** Citrate esters

such as triethyl citrate and acetyl tributyl citrate are biodegradable, relatively non-toxic in nature, and can be safely applied on food packaging and toys. Compared with DEHP, its environment profile is relatively good. Consumer products have gained popularity very quickly [34].

4. **Epoxidized Soybean Oil (ESBO):** ESBO is a renewable source-based environmentally friendly alternative for use in applications. It is extensively used in food packaging and biomedical applications because it shows good biocompatibility with low toxicity [35].

Conclusion

The widespread usage levels of DEHP and its correlated toxicological effects make this one of the biggest concerns for public health and environmental safety. This is further elevated by the characteristics that also make DEHP an endocrine disruptor, as well as its likely reproductive effects, neurotoxicity, hepatotoxicity, and cardiotoxicity. Strong regulatory actions are highly needed and safer alternatives should be developed - current alternatives to DEHP include DINP, DOTP, citrate esters, among others whose promising results notwithstanding research in these areas is needed to better evaluate their long-term safety profiles. The consumption of DEHP as well as its alternatives must be monitored from time to time by governments and regulatory bodies to provide guarantees for human health and safety while taking into consideration the environmental implications of these chemicals.

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Ethical Approval

The study did not involve any human or animal testing.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

BAR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing-original draft; PVR: Investigation, Methodology, Resources, Software; MSR: Supervision, Validation, Visualization, Writing-review & editing.

All authors have read and agree to the published version of the manuscript.

Availability of Data and Materials

Please contact the authors for data requests.

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