Impact of Phthalates on Reproductive Health of Man

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Key points

- Phthalates are 1,2-benzene carboxylic acid dialkyl or alkyl esters. They are formed through the reaction between alcohols and with the carboxyl groups present on the benzene ring of phthalic acids.
- Phthalates belong to the chemicals known as Endocrine Disrupting Chemicals (EDCs).
- Phthalates are man-made chemicals used in the plastic industry. Phthalates are mainly exposed to humans via inhalation, ingestion, and trans-placental route.
- Phthalates can disrupt testosterone production and sperm quality and function thus negatively affecting reproductive health.

Phthalates are a class of compounds frequently used to increase the flexibility and durability of plastics such as polyvinyl chloride (PVC). Phthalates, also known as phthalic acid esters (PAEs), are 1,2-benzene carboxylic acid dialkyl or alkyl esters (1). Phthalate esters are generated through the reaction between alcohols such as methanol, ethanol, or other similar compounds, with the carboxyl groups present on the benzene ring of phthalic acids. Various alkyl chains are made, forming the corresponding esters, such as dimethyl phthalate (DMP), dibutyl phthalate (DBP), and di(2-ethylhexyl) phthalate (DEHP). They differ in composition and structure and are hydrophilic by nature. In general, phthalates exhibit a molecular weight ranging from 194 to 396, accompanied by relatively low melting points that span from -4.6°C to 5.5°C (2). Between 1970 and 2006, their global production increased from 1.8 to 4.3 million tons, and it is still increasing rapidly (3).

Since PAEs are everywhere in our environment, the primary sources of human exposure are food contamination, food packaging, tablecloths, medical devices, plastic toys, cosmetics, wall coverings, nail polish, perfumes and deodorant. Phthalates have the potential to be absorbed by all parts of the human body, and they can even cross the placenta, negatively influencing the fetus and neonates. Detectable levels of phthalate esters have been found in food, human mother's milk, dust, environmental samples (soil, sediment, water), and textiles, with di (2-ethylhexyl) phthalate (DEHP) and di-n-butyl phthalate (DBP) being the most abundant. In general, phthalates exhibit low levels of acute toxicity and have relatively short biologic half-lives, typically ranging from 6 to 12 hours (4). Human vertebrates metabolize and eliminate these substances within 48 hours of exposure, indicating that they do not exhibit significant bioaccumulation in the system (2). Numerous scholarly investigations have been conducted to examine the correlation between phthalate exposure and male reproductive health, particularly in relation to sperm count. These studies have indicated a potential association between elevated phthalate exposure and diminished sperm count, along with other detrimental impacts on sperm quality and functionality (5,6). Therefore, the potential adverse effects on human reproduction and development can be attributed to the endocrine-disrupting properties of certain phthalates.

Phthalates have the potential to disrupt male reproductive health through various mechanisms.

1. The phthalate mono-(2-ethyl-hexyl) phthalate (MEHP), inhibit the synthesis of Sterogenic Acute Regulatory Protein (STAR), which plays a crucial role in facilitating the transportation of cholesterol to the mitochondria of Leydig cells for testosterone production. MEHP also exert a suppressive effect on the production of p450scc, an essential enzyme in the synthesis of testosterone, which is responsible for converting cholesterol to pregnenolone (7,8).
2. Additionally, MEHP alters the spermatogenesis by decreasing proliferation of Sertoli cells (nourishes the growing sperm cells during spermatogenesis), alteration of gonocyte- gonadotrophin interactions, and activation of testicular apoptosis by increased Fas ligand expression (9).
3. MEHP, the reactive metabolite of di(2-ethylhexyl) phthalate (DEHP), stimulates retinoid X receptor heterodimers in a competition for binding sites on DNA and restricts the availability of coactivators necessary for aromatase gene transcription (an enzyme

implicated in testosterone synthesis), thus impeding the transcription of aromatase, an enzyme critical for sexual development (8).

4. Another phthalate called dibutyl phthalate (DBP) lowers the levels of fetal plasma cholesterol, which in turn causes low fetal testosterone synthesis. This can negatively impact testicular descendance and secondary sexual characteristics. Furthermore, prenatal exposure to the phthalates can lead to testicular dysgenesis syndrome (TDS) (10).

Overall, the available evidence suggests that phthalates can disrupt testosterone production and sperm quality in males through various mechanisms, including alterations in Leydig cell function, gonocyte development, and gene expression involved in steroidogenesis and testis descent. The effects of phthalates on male reproductive health may be cumulative and dose-additive, and early-life exposure to phthalates may have long-term impacts on reproductive health. Further research is needed to comprehensively understand the mechanisms of action and potential health effects of phthalates on male reproductive health.

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