The Effects of Parental Phthalate Exposure on Newborn Defects

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ABSTRACT

Phthalates, or phthalate esters, are employed in the making of numerous products around the world, such as food containers, children's toys, detergents, surfactants, household items, and even pharmaceutical tablets. With the flexibility, elasticity, and inexpensive price, companies started using phthalates without doubting their acute and chronic toxicity. Recent research suggests that phthalate esters are possible causes of asthma, obesity, type II diabetes, neurodevelopmental issues, heart diseases, cancer, and especially reproductive system issues. However, studies about the effects of phthalates on fetal development are rare. To summarize updated data on this field, this review poster covers the most prominent *in vivo* studies, both animal models and humans, regarding phthalates exposure during pregnancy to newborn defects. Additionally, novel hypotheses on molecular mechanisms and important suggestions are provided to minimize possible negative outcomes of phthalate applications.

BACKGROUND

A – WHAT IS PHTHALATES?

- In the 1920s, phthalates, the dialkyl or alkyl esters of phthalic acid, were first created and introduced (1,2).
- The ideal materials due to their liability, elasticity, low volatility, and efficiency at a reasonable cost (3).

B – WHERE CAN WE FIND PHTHALATES?

- The world consumed more than 7 million tonnes of phthalates every year (5).
- In wire and cable, car, personal-care products, cosmetics, latex adhesives, inks and dyes, food wrapping materials, kitchen and home furnishing, clothing, children's toys, food-related goods, and pharmaceutical coating (6,7).

C – WHAT ARE PHTHALATES' EFFECTS ON HEALTH?

- Phthalates and PVC are actually mixed and blended without any covalent bond (1).
- Easy to migrate into the surface of PVC (3).

=> The particles can release by physical effects (friction, heating, or extraction with organic solvents), diffuse into the air, water, or food, and be exposed to users via inhalation, ingestion, or dermal contact.

=> May cause asthma, liver and reproductive diseases, and cancer (3,4). Phthalates once are named endocrine-disrupting chemicals (EDCs).

D – THE KNOWLEDGE GAP?

- Many studies show associations between nutrition factors on newborn defects.
- Phthalates can overcome the placental barrier (8).
- Only a few studies are about the effects of phthalates on fetal development.

OBJECTIVES

WHAT IS KNOWN?

- Phthalates induce diseases (e.g. asthma, liver and reproductive issues, cancer) in children and adult health.
- Phthalates can overcome the placental barrier.

WHAT THIS STUDY ADDS?

- Summary about effects of phthalates during pregnancy on newborn defects.
- Novel hypothesis on molecular mechanism and future suggestions.

METHOD

Two databases are exploited including Google Scholar and PubMed. The search term for both are *"phthalates" OR "phthalate esters" OR "phthalates toxicity" AND "newborn defect" OR "newborn malformation" OR "fetal malformations"*. No filter or year limitation is applied. The research was conducted during March 2022.

To ensure objectivity, this report follows the PEO framework with question format of Population (sample size and target population), Exposure (phthalate types and dose), and Outcome (main findings).

RESULTS

10 trustworthy papers were selected and reviewed. 4 articles are experiments on animals **(Table 1)**, and the rest 6 articles are human studies **(Table 2)**.

TABLE 1

Article	Sample size	Model	Experimental methods	Phthalate	Dose	Main findings
ShengZhao et al., 2019 (9)	20 female rats: control and DBP-exposed groups	Sprague-Dawley rat	Gene chip analysis, histology and immunohistochemistry, real-time PCR, Western blot, measurement of intracellular ROS	DBP	750 mg/kg	- Maternal exposure to DBP inhibited hedgehog signaling pathway via HhIP protein in newborn males. - Molecular mechanism identification: affects the ROS-HhIP-Gli1-autophagy axis and induces abnormal autophagy in uroepithelial cells.
Xiyan Mu et al., 2020 (10)	Three groups: control, 50 µg/L exposed, and 250 µg/L exposed groups	Wild-type Danio rerio zebrafish	Illumina sequencing and transcriptomic analysis, methylated DNA immunoprecipitation sequencing (MeDIP-Seq), real-time PCRs, qPCR, ELISA	DEHP and DBP	50 µg/L and 250 µg/L	- DBP and DEHP maternal exposure increased cardiac birth defects (abnormal heart rate and pericardial edema). - Molecular mechanism identification: changes in developmental gene expression (transcriptional alterations by modified DNA methylation of tbx5b, nppa, ctnt, my17, cmlc1) and abnormal cell apoptosis.
Le Qian et al., 2020 (11)	Three groups: control, 50 µg/L exposed, and 250 µg/L exposed groups	Wild-type (AB) zebrafish	qPCR analysis, real-time PCR	DEHP and DBP	50 µg/L and 250 µg/L	- Embryonic exposure of zebrafish to DEHP and DBP generated spinal birth defects and spine deformation. - Molecular mechanism identification: the alteration of development-related gene expression - notochord (col8a1a and ngs), muscle (stac3, klhl41a and smyd2b) and skeleton (bmp2, spp1).
Xiyan Mu et al., 2018 (12)	Three groups: control, 50 µg/L exposed, and 250 µg/L exposed groups	Wild-type (AB) zebrafish	Illumina sequencing and transcriptomic analysis, proteomics, lipidomics, ELISA, gene expression analysis	DEHP and DBP	50 µg/L and 250 µg/L	- DEHP and DBP caused a set of abnormal effects including decreased body length, yolk sac abnormities, immune response, estrogenic effects, and reduced lipid levels. - Molecular mechanism identification: changes in lipid metabolism, induces immune stress, generates estrogenic activation and hormone disruption.

TABLE 2

Article	Sample size	Study design, target population	Experimental methods	Phthalate	Collection	Main findings
Chung-Hsing Chen et al., 2018 (13)	64 infant–mother pairs	Birth cohort study, infant–mother pairs	Measurement of phthalate exposure, DNA methylation level analysis, liquid chromatography tandem–mass spectrometry (LC–MS/MS), pyrosequencing	DEHP, mono (2-ehtylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP)	Urine samples, cord blood samples, questionnaire and birth record	- Maternal phthalate exposure induces antiandrogenic effect, abnormal spermatogenesis, and higher risk of cancer, abnormal cell cycle and cell proliferation, and protein secretion problems. - Molecular mechanism identification: DNA methylation changes in CpG sites of genes, especially PA2G4, HMGCR, and XRCC6 genes - in the gene set HALLMARK_ANDROGEN_RESPONSE.
Vince Fazekas-Pongor et al., 2020 (14)	A total of 577 cases of congenital heart defects and 1731 controls	Case–control study, newborns < 3 months	Large data collection and analysis on congenital anomalies and phthalate exposure, pregnancy-related questionnaire analysis	Not specific	Questionnaires (job-exposure matrix (JEM)-assessed and self-reported occupational exposures) and data reported from clinicals	- Paternal phthalate exposure has high connection with atrial septal defects.
Lulu Song et al., 2019 (15)	746 mother–newborn pairs	Birth cohort study, infant–mother pairs	Telomere length (TL) measurements by quantitative real-time PCR, phthalate metabolite measurements	MEOHP, MEHP, MEHHP, mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-ethyl phthalate (MEP), and mono-butyl phthalate (MBP)	Urine samples and cord blood samples	- Molecular mechanism identification: maternal phthalate exposure is associated to shorter TL in newborns.
Sheela Sathyanarayana et al., 2016 (16)	371 male newborn-mother pairs	Pregnancy cohort study, infant–mother pairs	Phthalate measurements by mass spectrometry, genital measurements	MEHP, MEOHP, MEHHP, MBP, mono-2-ethyl-5carboxy pentyl (MECPP), and monobenzyl phthalate (MBzP)	Urine and serum samples, questionaires	- DEHP exposure induces abnormal genital development and leads to increased incidence of hydrocele.
Gwen Tindula et al., 2018 (17)	265 mother–newborn pairs	A longitudinal birth cohort study, infant–mother pairs	Quantification of DNA methylation by pyrosequencing, phthalate metabolite concentrations, gene expression analysis by two-step RT-PCR	- Three low molecular weight metabolites: MEP, MBP, MiBP - Four DEHP metabolites: MEHP, MEHHP, MEOHP, MECPP - Four high molecular weight metabolites: MBzP, mono[3-carboxypropyl] phthalate (MCPP), monocarboxyoctyl ph thalate (MCOP), monocarboxynonyl phthalate (MCNP)	Whole cord blood samples, questionaire, and maternal urine samples	- Molecular mechanism identification: maternal phthalate exposure relates to dysregulations in DNA methylation of mostly MEG3 genes.
Ling Wang et al., 2021 (18)	157 women with fetal malformations (case group) and 147 women with normal fetuses (control group).	Cohort study, infant–mother pairs	High-performance liquid chromatography-mass spectrometry (HPLC-MS), normal fetal ultrasound, neonatal physical examination, and chromosome examination	MEP, MBP, MiBP, MEHP, MEHHP, MECPP, MEOHP, and MBzP.	Urine samples, and demographic data from questionnaires	- High levels of phthalate exposure in pregnant women relates to fetal malformations, including structural malformations (hydrocephalus, anencephaly, meningocele, tetralogy of Fallot, endocardial cushion defect, single ventricle, double outlet of right ventricle, transposition of great arteries, pulmonary artery stenosis, atrial and ventricular septum defects, lip/cleft palate, diaphragmatic hernia, pulmonary cystadenoma, pulmonary sequestration, bilateral renal dysplasia, polycystic kidney, inborn micromelia, osteogenesis imperfecta, and multiple malformations) and chromosome abnormalities (trisomy 21 syndrome, trisomy 18 syndrome, and deletion or duplication of chromosome fragments).

INCLUSION CRITERIA

1. All peer-reviewed studies about phthalate effects during pregnancy term on fetal defects.
2. No restrictions in species, demographic distributions, country, age, gender, or study design.

EXCLUSION CRITERIA

1. Abstract-only and no-full-text-available articles.
2. Review, letter, and pre-printed articles.
3. Not-written in English articles.
3. All articles which contain unreliable, reliably extracted, duplicated data.

DISCUSSION

A – PHTHALATES' IMPACT ON FETAL DEVELOPMENT

Phthalate exposure during pregnancy has a close connection with newborn malformations, including structural malformations (e.g. atrial septal defects, hydrocephalus, anencephaly, lip/cleft palate, pulmonary cystadenoma) and chromosome abnormalities (e.g. trisomy 21 syndrome, trisomy 18 syndrome).

B – MOLECULAR & CELLULAR MECHANISMS

- Induce more oxidative stress, abnormal cell cycle and cell proliferation.
- Change protein production and secretion pathways.
- Notochord signaling disruption in embryo development.
- Shorter telomere length and dysregulation in DNA methylation of major developmental genes (e.g. HMGCR, MEG3).

=> More about gene expression regulation through epigenetic mechanisms rather than gene mutations.

C – ACTUAL SITUATION & SUGGESTION

- 13 phthalate metabolites are detected in the urine of more than 2,500 people (5).
- Phthalates are responsible for more than 90,000 deaths/year in only America. Up to 47.1 billion dollars are lost per year.
- Major daily applications in pharmacy, medicine, cosmetics, and food industry still employ phthalates, especially in developing countries such as Vietnam, Taiwan, and India.

=> More efforts and attention from policymakers and governments should be put as a matter of citizens' health with clearer guidelines and labels.

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REFERENCES