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Review

# Obstetrical outcomes and biomarkers to assess exposure to phthalates: A review

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ABSTRACT

Studies of the effects on pregnancy outcomes of in utero exposure to phthalates, contaminants that are widely present in the environment, have yielded conflicting results. In addition, the mode of assessment of exposure varies between studies. The aim of this review was therefore to establish a current state of knowledge of the phthalates and metabolites involved in unfavorable pregnancy outcomes. Extant data were analyzed to determine which biomarker is the best suited to assess the relation between in utero exposure to phthalates and pregnancy outcomes.

This review of the literature was conducted using the database of PubMed. A search was made of studies investigating exposure to phthalates and the following birth outcomes: preterm birth (gestational age <37 weeks), change in gestational age, change in body size at birth (birth weight, length, head circumference), anti-androgenic function, decreased anogenital distance, cryptorchidism, hypospadias and congenital malformation. The methodological approach adopted in each study was examined, in particular the methods used for exposure assessment (biomarkers and/or questionnaire).

Thirty-five studies were included. Premature birth and decreased anogenital distance were the most commonly reported outcomes resulting from a moderate level of exposure to phthalates. The principal metabolites detected and involved were primary metabolites of di-2(ethylhexyl)-phthalate (DEHP) and di-*n*-butyl-phthalate (DnBP). No clear conclusion could be drawn with regard to gestational age at birth, body size at birth and congenital malformations. In epidemiological studies, maternal urine is the most suitable matrix to assess the association between in utero exposure to phthalates and pregnancy outcomes: in contrast to other matrices (cord blood, amniotic fluid, meconium and milk), sampling is easy, non-invasive and, can be repeated to assess exposure throughout pregnancy. Oxidative metabolites are the most relevant biomarkers since they are not prone to external contamination. Further epidemiological studies are required during pregnancy to i) determine the role of phthalates other than DEHP [currently replaced by various substitution products, in particular diisononyl-phthalate (DiNP)]; ii) establish the effect of phthalates on other outcomes (body size adjusted for gestational age, and congenital malformations); iii) determine the pathophysiological pathways; and iv) identify the most suitable time for biomarker determination of in utero exposure to phthalates.



**Contents**



*Abbreviations:* AF, amniotic fluid; AGI, anogenital index; AGD, anogenital distance; BMI, body mass index; BW, birth weight; CB, cord blood; CHD, congenital heart defects; CI, confidence interval; HMW-phthalates, high-molecular-weight phthalates; Insl3, insulin-like factor 3; JEM, job-exposure matrix; LMW-phthalates, low-molecular-weight phthalates; MU, maternal urine; MW, molecular weight; nd, not detectable; OEP, occupational exposure prevalence; OR, odds ratio; ORa, adjusted odds ratio; PPARs, peroxisome proliferator activated receptor; PVC, polyvinyl chloride; T3, triiodothyronine; T4, thyroxine; ∑DEHP, summed DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP); ∑DiNP, summed DiNP metabolites (MHiNP, MOiNP, MCOP).

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## 1. Background

### 1.1. Origin and sources of exposure to phthalates

Phthalates are a family of chemical products made up of dialkyl esters or alkyl and aryl esters of orthophthalic acid (1,2-dicarboxylic acid) (Fig. 1). They are obtained by reacting orthophthalic acid with various alcohols ranging from methanol to tridecanol. Phthalates differ in the length of their carbon side chain, the lipophilicity of the molecule increasing with the length of the carbonated alcohol-chain. They are commonly divided into two groups according to their molecular weight on the basis of common properties such as their metabolism and similar industrial use (Table 1). High molecular weight (HMW) phthalates, such as DiDP, DiNP and DEHP, are widely used in industry as plasticizers to soften polyvinyl chloride (PVC). There are multiple sources of exposure to HMW-phthalates such as food packaging, bottled water, children's toys, medical devices, flooring, and building materials. Low molecular weight (LMW) phthalates, such as BBP, DnBP, DiBP, DEP and DMP, are used in paints, inks, adhesives, solvents, insecticides, body-care products (cosmetics, perfumes) and medications (Guo and Kannan, 2013; Hubinger, 2010; Schettler, 2006; Xu et al., 2010). Phthalates are commonly found in the home environment owing to the direct release, migration, leaching, evaporation and abrasion of and from PVC products. Hence, phthalates are ubiquitous environmental contaminants and humans are susceptible to exposure by ingestion, inhalation and dermal absorption.

### 1.2. Metabolism of phthalates and biomonitoring

Phthalates are non-persistent contaminants in the organism, where diesters of phthalic acid, because of their short half-life, are rapidly metabolized. Both LMW and HMW phthalates diesters are hydrolyzed into primary metabolite monoester phthalate, in a process catalyzed by lipases and esterases in the intestine and parenchyma. HMW-phthalates also undergo a series of secondary metabolizations (principally hydroxylation and oxidation), which give rise to secondary oxidative monoesters, and then undergo a phase of glucuro-conjugation. Conjugates are easily excreted in urine. LMW-phthalates are mainly excreted in urine as simple monoester phthalates while HMW-phthalates are mainly excreted in urine as oxidative monoester phthalates (Frederiksen et al., 2007; Koch et al., 2003; Wittassek et al., 2011). Some metabolites of phthalates and their fractional excretion in urine are summarized in Table 1.

Metabolites are chiefly excreted in urine and thus exposure to phthalates is in most cases assessed by the use of urine biomarkers (Hauser et al., 2004; Högberg et al., 2008). Other matrices have also been used, including blood, cord blood, amniotic fluid (AF), meconium and maternal milk (Huang et al., 2009; Latini et al., 2003; Main et al., 2006; Zhang et al., 2009). The review of Wittassek et al. (2011) gives a detailed description of the human biomonitoring of phthalates.

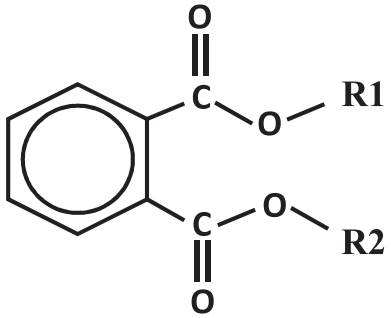


**Fig. 1.** Chemical structure of phthalates. R1 and R2 express the aryl or alkyl groups.