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Maternal exposure to di-2-ethylhexylphthalate and adverse delivery outcomes: a systematic review

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Abstract

Adverse pregnancy outcomes, including preterm delivery, short gestational age, and abnormal birth weight, remain a public health concern. The evidence on the association of the most common phthalate, di-2-ethylhexyl phthalate (DEHP) with adverse pregnancy outcomes remains equivocal. This systematic review summarizes published studies that investigated the association of DEHP with preterm delivery, gestational age, and birthweight. A comprehensive literature search found 15 relevant studies, most of which evaluated more than one outcome (four studies for preterm delivery, nine studies for gestational age, and ten studies for birthweight). Studies varied greatly with respect to study design, exposure assessment, analytical methods, and direction of the associations. We identified important methodological concerns which could have resulted in selection bias and exposure misclassification and contributed to null findings and biased associations. Given limitations of the previous studies discussed in this review, more thorough investigation of these associations is warranted to advance our scientific knowledge.

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Keywords

preterm delivery; birthweight; phthalate exposure; gestational age

1. Introduction

Phthalates are industrial chemicals extensively used in a variety of consumer products, including plastic food containers, cosmetics/beauty products, toys, and certain medical products such as blood bags and pharmaceutical coatings [1]. Because of their wide-spread use and biological effects in animals, phthalates were included in the list of regulated (priority) pollutants by the US Environmental Protection Agency and the European Union [2]. Humans are exposed to phthalates through ingestion, inhalation, and dermal contact as well as via parenteral route when using medical devices [1]. Phthalates have short biological half-lives (6-12 hours), metabolize quickly, do not bioaccumulate, and are primarily excreted in urine [1, 3]. Secondary phthalate metabolites are detected in 100% of the samples from general US population with wide variation [4, 5]. Further, higher levels of phthalates in younger women as compared to men of the same age have been also reported possibly reflective of their potential exposure from cosmetic products [6].

Di-2-ethylhexyl phthalate (DEHP) is the most common phthalate that the general population is exposed to ubiquitously mainly through ingestion [7, 8]. DEHP is rapidly hydrolyzed in the intestine to the corresponding monoesters (mono-(2-ethyl-hexyl) phthalate, MEHP) [7, 9, 10]. These monoesters are considered the biologically active metabolites and their use as biomarkers of DEHP exposure minimizes accidental contamination from parent compound [11-13]. In addition, urinary concentrations integrate exposures from multiple routes thus accounting for the total exposure [14]. Upon absorption, these monoesters undergo further hydroxylation and oxidation (Figure 1) [7]. A greater proportion of the dose of DEHP is represented by the more downstream metabolites, including mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) [15, 16]. In addition, it has been previously shown that a higher ratio of MEHP to MEHHP or MEHP to MEOHP is associated with potentially greater endocrine disrupting capacity [7].

Animal studies have found a variety of adverse effects from exposure to phthalates, including DEHP. Most severe of these effects were noted for reproductive system and normal development. In animal studies, reduction in testosterone levels following administration of DEHP in male animals resulted in underdevelopment of various androgen-dependent tissues and testicular abnormalities including reduced anogenital distance, agenesis of the gubernacular cords and sex accessory tissues, undescended testis, epididymal agenesis, testicular atrophy, and others [13, 17, 18]. Some of these effects resemble testicular dysgenesis syndrome in humans [14]. In female animals, reproductive effects from phthalates included altered serum estradiol levels, advanced or delayed onset of puberty, increased ovarian and uterine weights, and deficits in growing follicles and corpora lutea [14]. Other effects observed in one or more animal species included changes in hepatic

structure and function, including liver cancer, changes in kidney function, and disruption of thyroid signaling, immune functions, and metabolic homeostasis [13, 14, 19-25].

The evidence on the association of phthalates with adverse effects in humans is limited. Previous studies suggested an association of exposure to phthalates with the risk of premature thelarche [26, 27], higher risk of endometriosis [14, 28, 29], low sperm quality [11, 30, 31], reduced testosterone levels [32-34], obesity, diabetes, and possibly breast cancer [12, 35-41]. Given the variety of these effects and ubiquitous exposure, phthalates were included on the list of endocrine-disrupting compounds with high exposure concern, evidence of endocrine disruption, and highest priority for research [42]. Moreover, phthalates have been recently classified by the International Agency for Research on Cancer as possible carcinogens to humans [43].

Several biological mechanisms were suggested for reproductive and developmental toxicity of DEHP. The primary metabolite of DEHP, MEHP, is a well-known ligand for the peroxisome proliferator-activated receptor (PPAR) family [14, 44], is a mitochondrial toxicant and disruptor of lipid and glucose metabolism [14, 44-46], and is the most potent DEHP metabolite in its toxicity [14, 47, 48]. Even though some studies suggested differences in susceptibility to the toxic effects of peroxisome proliferators across species with lower potential in humans, the basis for species differences in peroxisome proliferation and carcinogenesis by phthalate esters has not been fully described [13, 48]. In addition, phthalates were also found to reduce the expression of insulin-like factor 3 (insI3) gene involved in the initial stages of testicular descent [14]. In females, DEHP-induced activation of PPAR resulted in dysregulation of aromatase activity and decreased estradiol production in rat granulosa cells [14]. Finally, a growing body of evidence suggests that, in addition to endocrine-disrupting effects on reproductive system, DEHP exhibits pro-inflammatory properties [49-53] and is associated with thyroid dysfunction [54-57]. Importantly, inflammation, oxidative stress, and hypothyroidism, all have been associated with adverse pregnancy outcomes in previous studies in humans [58-61].

The role of prenatal exposures with endocrine disrupting potential, including phthalates, on pregnancy outcomes is poorly understood. Adverse pregnancy outcomes, including preterm delivery, short gestational age, and abnormal birth weight, remain a public health concern [62, 63]. These outcomes are associated with an increased risk of morbidity and mortality in the first year of life [64] as well as long-term health consequences in childhood and adulthood, such as neurodevelopmental disability, an increased risk of behavioral problems, hypertension, type 2 diabetes, cardiovascular disease, obesity, psychiatric disorders, and cancer [65-70].

The purpose of this systematic review was to summarize published studies on the association of exposure to DEHP, the most common phthalate, with preterm delivery, gestational age, and birthweight in humans and to identify methodological gaps that need to be addressed in future studies.

2. Materials and Methods

2.1 Literature search, study selection, and data extraction

An electronic search was performed using PubMed Central (U.S. National Institutes of Health [NIH]), BioMed Central, and Toxnet with the cutoff date of July 31, 2015. Bibliographies of the articles identified in the electronic searches were then searched manually for additional relevant references. We used any combination of the key words/terms “DEHP” ‘MEHP’, ‘MEHHP’, ‘MEOHP’, ‘MECCP’, ‘DEHP metabolites’ with “gestational age”, “preterm delivery”, “birth weight”, and “birthweight” to identify relevant publications.

Study selection was accomplished by first applying the following inclusion criteria: (1) accessible in full-text manuscript and (2) published in English. We then excluded studies that did not measure DEHP metabolites in biological specimens to objectively characterize the exposure (referred to as exposure biomarkers or direct exposure assessment method). Our search yielded 117 manuscripts, from which 17 studies were relevant to the topic and met the eligibility criteria (Figure 2). Two studies were further excluded due to the absence of objective exposure assessment (biomarkers of exposure) [71, 72]. Two articles reported the results on the exactly same study population [73, 74] and thus only one was included in the review [73]. From each selected article, we extracted the data on epidemiologic design features including study type, sample size, characteristics of the study population, exposure assessment approaches (type and timing of biological specimen, measured DEHP metabolites), outcome assessment method, statistical analysis methods, and results for each of the studies outcomes. We examined the evidence of the association between DEHP exposure and the birth outcomes across the studies while grouping them by the type of the outcome and phthalate analyte.

3. Results

In Table 1, we summarize the key characteristics of the 15 studies included in this review. Most of the studies were prospective cohorts (9 studies or 56%), three studies utilized a nested case-control design, one study was case-control, and two studies were cross-sectional. Most of the studies simultaneously evaluated more than one adverse outcome, totaling 4 studies for preterm delivery, 9 studies for gestational age, and 10 studies for birthweight. The mean sample size across the studies was 307 with a median of 283 women. Five of the studies included racially/ethnically diverse study populations and the remaining 10 studies were limited to a single race/ethnicity (5 Asian, 3 Caucasian, and 2 Hispanic). Most of the studies (13 out of 15) used medical records to verify the pregnancy outcomes. All of the studies, except one, measured one or more DEHP metabolite in a biological sample; one study assessed parent DEHP concentrations only [75]. Selected studies additionally assessed associations of the birth outcomes with sum of DEHP metabolites (MEHP, MEHHP, MEOHP, and MECCP) or % MEHP (ratio of MEHP to the sum of MEHHP, MEOHP, and MECCP). Most of the studies (11 out of 15) measured phthalates in urine (spot urine or repeated samples). Other types of biological specimens included umbilical cord blood, maternal blood, meconium, and placental tissue. The details of the study designs and methods are summarized in Table 2.

Preterm delivery was defined as <37 weeks of gestation across all the studies. The results of these studies by the type of DEHP biomarker are presented in Figure 3. Across four studies that evaluated the association of DEHP with preterm delivery, one study [76] reported significant inverse associations with MEHP, MEHHP, and MEOHP, and three studies reported significant positive associations with MEHP, MECPP, and parent DEHP concentrations [34, 73, 75].

Figure 4 summarizes the results of the studies on the association of gestational age with DEHP. Four of the nine studies found inverse associations of all individual metabolites, Σ DEHP, and parent DEHP with gestational age and two studies reported positive associations with MEHP, MEHHP, and MEOHP.

The results of the studies on the association of birthweight with phthalates are presented in Figure 5a (findings reported as regression coefficients) and 5b (findings reported as odds ratios), with the exception of three studies that did not report risk estimates [77-79]. Among ten studies, two reported significant inverse associations of MEHHP or DEHP with birthweight [75, 80] and two studies found positive associations with MEHP, MEHHP, and MEOHP [81, 82].

4. Discussion

The evidence on the association of phthalates with adverse birth outcomes remains inconsistent. We systematically reviewed 15 published studies that investigated the association of the most common phthalate, DEHP, with preterm delivery, gestational age, and birthweight. We identified important methodological concerns (discussed below) related to different aspects of study design which could have resulted in selection bias and exposure misclassification and contributed to null findings and biased associations in the identified studies. We further discussed their implications and suggested some strategies for the future studies.

4.1 Study population and sample size

The median sample size across the studies was relatively small (283 women) and given that the relative increase in the risk associated with environmental exposures is usually low, typically below 1.5 [83], these studies were likely underpowered to detect significant associations. In addition, some of the studies were focused on high-risk populations thus limiting generalizability of their findings. For example, Philippat et al. included pregnant women who gave birth to infants with malformations and their matched controls [84]. Another study by Huang et al. included women who had indication for amniocentesis due to advanced maternal age and abnormal screening [78]. This study subsequently reported a significant inverse association of DEHP with birthweight and gestational age and a higher risk of preterm delivery in women with higher DEHP levels, which should be interpreted with caution.

The majority of the identified studies were limited to a single race/ethnicity. Previous studies show disparities in distribution of selected phthalates among reproductive aged and pregnant women [85, 86] with higher levels noted in non-Hispanic Black and Hispanic women,

though the ethnic disparities in DEHP or other high molecular weight phthalates among women are inconsistent with most studies reporting no differences and a few reporting higher levels in Caucasians [87]. Further, a recent study showed that non-Hispanic Blacks and Hispanic individuals had higher levels of %MEHP (the ratio of MEHP to the sum of the secondary metabolites), reflective of a slower MEHP conversion rate and possibly, higher potential for adverse effects from DEHP exposure [88]. Previous studies also demonstrated pronounced racial disparities in occurrence of adverse pregnancy outcomes including preterm birth and low birthweight [89, 90]. Finally, racial/ethnic differences in the associations of phthalates with adverse health outcomes such as diabetes have been also reported [91]. The above listed disparities make it important to examine these associations in racially diverse populations and to identify population subgroups that might be more susceptible to adverse effects of phthalates on pregnancy outcomes.

4.2 Exposure assessment

The studies varied with respect to the different aspects of exposure assessment, including the type of biological specimen, timing of sample collection, and the number of samples per woman.

Use of urine samples is the standard approach for biomonitoring of phthalates, including DEHP. Urine samples offer several advantages as compared to other types of biospecimens, including ease of sample collection, higher metabolite concentrations, and reduced potential for contamination by the parent compound and its subsequent conversion into metabolites as the result of post-collection enzymatic activity in the blood samples leading to hydrolysis of extraneous phthalate diesters to their monoesters and, subsequently, exposure misclassification [1, 7, 8, 11, 16, 92]. In the studies measuring concentrations in umbilical cord blood, contamination by DEHP in the sampling and analytic equipment cannot be excluded [93]. Furthermore, previous studies suggest that cord blood samples may not be reflective of maternal exposure levels during pregnancy (correlation between maternal and cord blood levels ranging between 0.1 and 0.5) [16]. Whenever possible, the use of urinary samples for exposure assessment should be preferred.

Even though DEHP is rapidly metabolized within hours (half-life 6-12 hours) [1, 3], previous studies suggest that a single urine sample can accurately reflect phthalate exposure over the previous 3 months [14, 94, 95]. However, previous reports suggest that metabolite concentrations have equivocal reproducibility in pregnant women, especially during the last 6 weeks of pregnancy (intraclass correlation for DEHP metabolites ranging from 0.30 to 0.36; for Σ DEHP = 0.08) [96, 97]. Thus, the use of a single sample in the studies assessing the exposure during the 3rd trimester (majority of the studies) could result in significant exposure misclassification. Collection of repeated samples (one per pregnancy trimester) to account for intra-individual variation in DEHP biomarker levels is strongly recommended. Further, standardization for the time of day may be needed to account for within-individual variability [11, 16]. Finally, it was previously reported that urinary creatinine excretion may be affected by individual characteristics, including age, muscle mass, and race, as well as lifestyle factors, such as diet and physical activity [16]. Creatinine excretion may vary during the course of pregnancy and specific gravity may be more effective in correcting for

urine dilution later in pregnancy as it is not influenced by individual factors, thus reducing the chances for exposure misclassification [16, 97, 98].

It remains unclear which window of susceptibility during pregnancy would be more relevant for the potential effect of phthalates on adverse birth outcomes. A recent report indicates that both early and late exposures during pregnancy could have implications for preterm birth [74]. Previous studies on the associations of other environmental exposures with birth outcomes suggest that exposures during the 2nd and 3rd trimester could have greater impact on birth outcomes, as the result of more rapid fetal weight gain in the 3rd trimester as well as disrupting effects of DEHP on parturition [76, 99, 100]. In some of the included studies, the samples were collected in the 1st trimester while others have varied sample collection timing [77, 78, 80, 84]. In addition, some of the effects of phthalates on selected outcomes, such as birthweight, could potentially result from “fetal programming” earlier in pregnancy leading to long-term effects on structure, physiology and metabolism [101-103]. For example, undernutrition in the 1st trimester of pregnancy has been linked to increased birth weight [102] suggesting possible importance of this crucial period for metabolic programming. Thus, exposure assessment during different windows of susceptibility is warranted for better understanding of the effects of DEHP exposure on birth outcomes.

It has been previously shown that a higher ratio of MEHP to MEHHP or MEHP to MEOHP is associated with a greater physiologic effect and potentially greater endocrine disrupting capacity as compared to individual metabolites [7]. It was also suggested that MEHP, but not other metabolites, can disturb energy metabolism of fat cells [104], a mechanism which could potentially lead to changes in birthweight. Only one study attempted to account for individual differences in phthalate metabolism by examining the ratio of MEHP concentration to the sum of MEHHP, MEOHP, and MECPP (% MEHP). Using the ratios of metabolites rather than individual metabolite concentrations in future studies could help to account better for different metabolic patterns. Finally, even though the evidence from animal studies suggests transplacental transfer of MEHP [105], findings from the studies in humans have been conflicting [14, 106]. Thus, the results of the studies on maternal MEHP concentrations and birthweight should be interpreted with caution.

4.3 Important confounders

Previous studies suggest that several maternal factors and environmental exposures can affect birthweight and duration of pregnancy. Maternal weight gain during the 2nd and 3rd trimester, history of diabetes and gestational diabetes, and maternal smoking and alcohol use increase the risk of adverse birth outcomes [107-113]. However, only a few of the studies in this review accounted for possible confounding effect of these risk factors and some of the findings could be explained in part by the residual confounding effects. Adjustment for these risk factors in future studies is warranted.

5. Conclusions

We found no consistent evidence of the association of phthalates with preterm delivery, gestational age, and birthweight across the studies included in this review, which might be explained by the heterogeneity of the studies. Given the aforementioned methodological

gaps that likely contributed to the findings, addressing these concerns in more thorough investigation of these associations is warranted to advance our scientific knowledge on the potential effects of DEHP exposure on birth outcomes.

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Highlights

- The evidence on association of DEHP with adverse pregnancy outcomes is inconsistent
- Heterogeneity of the included studies precludes a direct comparison of the findings
- Some of the findings should be interpreted with caution due to design limitations
- Future studies should address methodological concerns identified in this review

Figure 1. Di-2-ethylhexyl phthalate (DEHP) metabolism

DEHP is rapidly hydrolyzed in the intestine to MEHP, which undergoes further hydroxylation and oxidation. A greater proportion of the dose of DEHP is represented by the more downstream metabolites, including MEHHP, MEOHP, and MECPP. MEHP, MEHHP, MEOHP, and MECPP are used as biomarkers of exposure to DEHP.

Abbreviations: MBP - monobutyl phthalate; MBzP - Mono-benzyl phthalate; MEHP - Mono-2-ethylhexyl phthalate; MEP - Mono-ethyl phthalate; MEHHP - Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate; MOEHP - Mono-2-(1-oxoethyl)hexyl-d4 phthalate; MCMHP - mono(2-carboxymethylhexyl) phthalate; MHEHP – mono-2-(hydroxyethyl)hexyl phthalate, MHECPP – mono-e-(1-hydroxyethyl)-5-carboxypentyl phthalate, MEHCPP – mono-(2-ethyl-4-hydroxy-5-carboxypentyl) phthalate, MEOCPP -mono-(2-ethyl-4-oxo-5-carboxypentyl) phthalate; MECBP – mono-(2-ethyl-4-carboxybutyl) phthalate, MHECBP – mono-2-(1-hydroxyethyl)-4-carboxybutyl phthalate, MECPrP - Mono(2-ethyl-3-carboxypropyl) phthalate

Figure 2. Flow diagram of literature search

Figure 3. Associations of phthalate metabolites with preterm delivery across the studies

Individual study results are presented by DEHP metabolites. Vertical lines represent odds ratios and corresponding 95% Confidence Intervals. as follows: per log unit change (*); per one quartile change (#), or for > vs. < median (‡) metabolite concentration. Abidi (2009) reported significant inverse associations with MEHP, MEHHP, and MEOHP, and Ferguson (2014), Meeker (2009), and Huang (2014) reported significant positive associations with MEHP, MECPP, and parent DEHP concentrations.

Abbreviations: MEHP-Mono-2-ethylhexyl phthalate; MEHHP-Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate, ΣDEHP-sum of metabolites

Figure 4. Association of phthalate metabolites with gestation age (weeks) across the studies

Individual study results are presented by DEHP metabolites. Note: does not include study by Lanini et al that reported ORs (for MEHP=1.50, 95% CI 1.01-2.21; does not include studies by Suzuki et al and Huang et al (2009) as the risk estimates are not reported. Vertical lines represent regression coefficients and corresponding 95% Confidence Intervals as follows: per log unit increase (*); per inter-quartile range increase (**), or per doubling of log2-transformed exposure levels (†). Four studies found inverse associations of all individual metabolites, ΣDEHP, and parent DEHP with gestational age and two studies reported positive associations with MEHP, MEHHP, and MEOHP.

Abbreviations: MEHP-Mono-2-ethylhexyl phthalate; MEHHP-Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate, ΣDEHP-sum of metabolites

Figure 5a. Associations of DEHP metabolites with birthweight (studies reporting regression coefficients)

Individual study results are presented by DEHP metabolites. Note: does not include study by Lanini et al., Suzuku et al., and Huang et al. (2009) as the risk estimates are not reported.

Vertical lines represent regression coefficients and corresponding 95% Confidence Intervals as follows: per log unit increase (*); per 1.70 ng/mL increment increase in ln(MEHHP) (**), or per doubling of log2-transformed exposure levels (†). Huang (2014) and Lenters (2003) reported significant inverse associations of MEHHP or DEHP with birthweight.

Abbreviations: MEHP-Mono-2-ethylhexyl phthalate; MEHHP-Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate, ΣDEHP-sum of metabolites

Figure 5b. Associations of DEHP metabolites with birthweight (studies reporting odds ratios)

Individual study results are presented by DEHP metabolites. Vertical lines represent odds ratios and corresponding 95% Confidence Intervals per log unit change (*). Zhang (2009) and Zao (2015) found positive associations with MEHP, MEHHP, and MEOHP.

Abbreviations: MEHP-Mono-2-ethylhexyl phthalate; MEHHP-Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; Σ DEHP-sum of metabolites

Summary Characteristics of the Studies on Association of DEHP Exposure With Preterm Delivery, Gestational Age, and Birthweight

Table 1

Study characteristic	Preterm delivery (n=4)		Gestational age (n=9)		Birthweight (n=10)	
	N (%)	Study sample range	N (%)	Study sample range	N (%)	Study sample range
Study design						
Nested case-control	2 (50%)	60-482	0	N/A	1 (10%)	119-201
Prospective cohort	1 (25%)	283	7 (78%)	65-404	6 (60%)	65-1250
Case-control	0	NA	0	NA	1 (10%)	201
Cross-sectional	1 (25%)	207	2 (22%)	84-207	2 (20%)	84-207
Racial/ethnic composition						
Caucasian only	0	NA	1 (11%)	84	3 (30%)	84-1250
Hispanic only	1 (25%)	60	2 (22%)	72-390	1 (10%)	390
Asian only	1 (25%)	207	3 (33%)	65-207	5 (50%)	65-207
Racially diverse	2 (50%)	283-482	3 (33%)	283-404	1 (10%)	404
Sample type						
Spot urine	2 (50%)	60-283	6 (67%)	65-404	5 (50)	65-404
Repeated urine	1 (25%)	482	1 (11%)	390	1 (10%)	390
Umbilical cord blood	1 (25%)	207	2 (22%)	84-207	3 (30%)	84-207
Maternal blood	0	NA	0	NA	2 (20%)	201-1250
Meconium	0	NA	0	NA	1 (10%)	201
Placental tissue	0	NA	0	NA	1 (10%)	119
DEHP metabolites measured						
MEHP	3 (75%)	60-482	8 (89%)	65-404	7 (70%)	65-404
MEHHP	3 (75%)	60-482	6 (67%)	72-404	6 (60%)	119-1250
MEOHP	3 (75%)	60-482	6 (67%)	72-404	6 (60%)	119-1250
MECPP	2 (50%)	60-482	3 (33%)	331-404	3 (30%)	287-404
DEHP	1 (25%)	207	2 (22%)	84-207	3 (30%)	84-390
All metabolites	2 (50%)	60-482	3 (33%)	331-404	2 (20%)	404

Abbreviations: DEHP, di-(2-ethylhexyl)phthalate; MEHP, mono - (2-ethylhexyl)phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl)phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl)phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl)phthalate

Table 2
Key Design Features of the Studies on Association Between DEHP Exposure and Birth Outcomes

Reference, country	Study Design	Sample Size ^a	Outcome assessed	Phthalates measured	Sample type and timing	Urine Dilution Correction	Confounders adjusted for
Lanini et al. 2003, Itali [79]	Cross-sectional	84	Gestational age Birthweight	DEHP, MEHP	Umbilical cord blood collected immediately after delivery	N/A	Not reported
Wolff et al. 2008, US [114]	Cohort	404	Gestational age Birthweight	MEHP, MEHHP, MEOHP, MECPP, ΣDEHP	Spot urine sample, 3 rd trimester	Creatinine	Race/ethnicity, infant sex, prenatal smoking, maternal pre-pregnancy BMI, education, and marital status, gestation age (for birthweight)
Adibi et al. 2009, US [76]	Cohort	283	Gestational age Gestational age >41 weeks Preterm birth (<37 weeks)	MEHP, MEHHP, MEOHP, % MEHP ^b	Spot urine sample, 3 rd trimester	Creatinine	Race, geographic site, mother's education, age, employment status during pregnancy, timing of urine sample, parity, history of miscarriage, infant sex, maternal and paternal smoking, job-related stress, mother's pre-pregnancy health
Zhang et al. 2009, China [81]	Case-control	88//113	Birthweight	MEHP, DEHP	Umbilical vein blood collected immediately after delivery; Maternal blood samples collected post-delivery Meconium: within 48 hours post-delivery	N/A	Gestational age, smoking at home, socioeconomic status, and pre-pregnancy BMI
Whyatt et al., US 2009 [115]	Cohort	331	Gestational age	MEHP, MEHHP, MEOHP, MECPP, ΣDEHP	Spot urine sample, 3 rd trimester	Specific gravity	Maternal ethnicity age, maternal pre-pregnancy weight and height, smoking during pregnancy, prenatal asthma, diabetes, and hypertension (yes or no), planned cesarean section (yes or no), and premature rupture of membranes (yes or no)
Meeker et al. 2009, Mexico [34]	Nested case-control	30//30	Preterm birth (<37 weeks)	MEHP, MEHHP, MEOHP, MECPP, ΣDEHP	Spot urine sample, 3 rd trimester	Creatinine, specific gravity	Marital status, maternal education, infant sex, and gestational age at time of urine sample
Huang et al. 2009, China [78]	Cohort	65	Gestational age Birthweight	MEHP	Spot urine samples, 15-20 minutes before amniocentesis (1 st trimester) Amniotic fluid collected at the beginning of amniocentesis	Creatinine	Not reported
Suzuki et al. 2010, Japan [77]	Cohort	149	Gestational age Birthweight	MEHP, MEHHP, MEOHP	Spot urine sample, 9 th to 40 th week of gestation	Creatinine	Infant sex, parity, maternal age, BMI and gestational age (for birthweight).
Philippat et al. 2012, France [84]	Cohort	287	Birthweight	MEHP, MEHHP, MEOHP, MECPP	Spot urine sample, collected at 6- 30 gestational weeks	Creatinine	Gestational age, maternal pre-pregnancy weight and height, maternal smoking, education, parity, recruitment center
Ferguson et al., 2013, US [73]	Nested case-control	130/352	Preterm birth (<37 weeks)	MEHP, MEHHP, MEOHP, MECPP, ΣDEHP	Repeated urine samples (1-3) throughout pregnancy	Specific gravity	Maternal age at first visit, race/ethnicity, education
Weinberger et al. 2014, US [116]	Cohort	72	Gestational age	MEHP, MEHHP, MEOHP	Spot urine sample, last clinic visit prior to delivery	Specific gravity	Parity and maternal race

Reference, country	Study Design	Sample Size <i>a</i>	Outcome assessed	Phthalates measured	Sample type and timing	Urine Dilution Correction	Confounders adjusted for
Huang et al. 2014, China [75]	Cross-sectional	207	Gestational age Preterm birth (<37 weeks) Birthweight	DEHP	Cord blood collected within 10 minutes of delivery	N/A	Maternal age, BMI, frequency of prenatal examination, pregnancy history, gestational age (for birthweight)
Lenters et al. 2015, Greenland, Poland, and Ukraine [80]	Cohort	1250	Birthweight	MEHHP, MEOHP, MECPP	Non-fasting venous blood sample at enrollment, varied timing	N/A	Maternal education, smoking during pregnancy, parity, birth season, and urinary cotinine levels during pregnancy
Casas et al. 2015, Spain [117]	Cohort	390	Birthweight Gestational age	MEHP, MEHHP, MEOHP, MECPP, ΣDEHP	Repeated urine samples, 1 st and 3 rd trimesters (12 and 32 weeks of gestation)	Creatinine	Site, maternal age, pre-pregnancy BMI, parity, gestational age (for birthweight), infant sex, maternal height, alcohol consumption before conception, maternal serum cotinine and serum vitamin D
Zhao et al. 2015, China [82]	Nested case-control	55/64	Fetal Growth Restricted Birth (birth weight <2,500 g and GA 37 weeks	MEHP, MEHHP, MEOHP	Spot urine sample, 3 rd semester Placental tissue samples collected immediately after delivery	Specific gravity	Infant sex, gestational age, environmental tobacco smoke during pregnancy

Abbreviations: BMI, Body Mass Index; DEHP, di-(2-ethylhexyl)phthalate; GA, gestational age; LMP, last menstrual period; MEHP, mono - (2-ethylhexyl)phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl)phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl)phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl)phthalate; ΣDEHP, sum of DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP); N/A, not applicable

*a*Total number for cohort studies, n of cases/n of controls for case-control studies

*b*Ratio of MEHP concentration to the sum of the secondary DEHP metabolite concentrations (MEHHP, MEOHP, and MECPP)