Review of epidemiological studies of the reproductive and developmental effects of exposure to *ortho*-phthalates published in 2014-2016

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This review is an update of a review completed in November 2013 (Rice, 2013). It is restricted to human (epidemiological) studies published in 2014-2016. It does not include toxicity studies in animal models or biochemical mechanistic studies designed to identify the biological perturbations underlying the effects of phthalates or phthalate metabolites. Sixty five studies were identified published in the last two years only related to the reproductive and developmental effects of *ortho*-phthalates. Investigators reported associations between phthalate exposure and numerous adverse outcomes, including deficits in both male and female reproductive fitness, physical changes in male genitalia at birth consistent with the anti-androgenic effects of phthalates, perturbations in timing of sexual maturation in children, and changes in neuropsychological function, metabolic homeostasis, and immune function. There is therefore mounting evidence that exposure to phthalates from environmental sources may result in adverse outcomes in a number of functional domains.

A number of issues are relevant to the interpretation of epidemiological studies assessing the potential effects of environmental phthalate exposure. There are a number of phthalates in commercial use, and human exposure is typically assessed by the presence of one or more metabolites of each of these parent compounds in the body, usually in urine but sometimes in blood or other bodily fluids. Phthalates do not stay in the body long, usually a few days at most. Therefore any measurement of phthalate concentration represents a "snapshot" of very recent exposure, which would bias results toward not finding an effect even if there were one. However, a number of studies documented a reasonably high consistency in body burden across time in individuals, presumably as a result of continuing exposure from the same sources. The total concentrations of phthalates in individuals, as well as the pattern of parent compounds or metabolites, varies across individuals, populations, and time (years) of assessment. In some countries such as the U.S., body burdens of older phthalates being phased out may be decreasing, whereas concentrations of more newly introduced phthalates are increasing (Table 1). Additionally, the levels and pattern of phthalate metabolites in the bodies of individuals differs between countries. Individual studies typically analyzed a number of metabolites of individual parent phthalates, but not necessarily the same metabolites or the same parent compounds. This adds further difficulty in comparing results from studies assessing the same or similar outcome measures. Therefore, the years that samples were collected, country of study, and number and identity of metabolites analyzed must be considered when interpreting individual studies and the

literature as a whole. Absolute consistency of results between studies with respect to which metabolites are associated with specific outcomes would not necessarily be expected.

As an example, a cohort of pregnant women from several U.S. cities recruited in 2010-2012 had concentrations of phthalates over three times lower than the same metabolites measured in a cohort recruited in 1999-2002 (Swan et al. 2015 [number 16 in Table 3], Swan et al.,2005). Moreover, seven metabolites were analyzed in the study published in 2005, and 10 metabolites were measured in the 2015 study. It is well established that a number of phthalates are anti-androgenic: i.e., they block the effects of testosterone. An effect that may be detected using non-invasive procedures is the distance between the external sex organs and anus, which is longer in males than in females. A decrease in anogenital distance in boys therefore represents a feminizing effect. Decreased anogenital distance in boys was observed in both U.S. studies related to maternal phthalate exposure, despite the differences in maternal body burden. Body burdens in pregnant Danish women in 2010-2012 were considerably lower than those in the 2010-2012 U.S. cohort (Jensen et al., 2106 [14 in Table 3]). In contrast to the effects observed in the U.S. studies, an effect on anogenital distance was not observed in the Danish study.

In Tables 2-5, which describe the results of individual studies, information is provided on the country in which the study was performed, the years in which the samples for phthalate analysis were collected, the specific metabolites analyzed, and the parent compound(s) those metabolites represent. Even though the current literature review was confined to the years of publication 2014-2016, it may be observed that samples were collected in some studies decades ago, whereas other studies represent exposure within the last 2-3 years. The metabolites analyzed also differ across studies, with a greater or fewer metabolites measured for a specific parent phthalate, as well as representing different parent compounds. Some investigators summed the metabolite levels in various ways, to represent metabolites of the same parent compound or family of parent compound phthalates (e.g. heavier vs. lighter). Other studies only compared outcomes to individual metabolites, which would potentially underestimate the effects of a particular parent phthalate.

Epidemiological studies can be classified into four basic designs. In studies in which birth outcomes are of interest, e.g., anogenital distance or size at birth, phthalate concentrations are measured in the mother during pregnancy and the outcome is measured at birth or shortly thereafter. Prospective studies measure the phthalate levels of women during pregnancy, and the offspring are followed into childhood. The phthalate levels at the time of testing during childhood may also be analyzed to determine whether concurrent phthalate exposure is related to outcome. In cross-sectional studies, phthalate exposure is assessed at the same time the outcome(s) is measured: for example, the relationship between the child's phthalate levels at the time of assessment and pubertal development. An additional cross-sectional design is the case:control design, in which cases with the outcome of interest are identified, and controls with the same relevant demographics are compared with respect to exposure.

It is well established that a number of phthalates interfere with the production of testosterone by acting on a number of enzymes and transporters. Therefore it is not surprising that a number of studies found an association between increased phthalate levels and reduced reproductive fitness in males (Table 2), including associations with both older and newer phthalates. Effects include increased pregnancy loss related to the man's phthalate levels [row 2 in Table 2]; longer time to pregnancy (1); decreased fecundity (1,8); a decrease in implantation (2); decreased sperm mobility (3,5), decreased sperm concentrations and semen volume (4,5,7,9), and an increase in abnormal sperm (4,5). Decreased testosterone levels and changes in chemical markers associated with reproductive fitness were also observed (6,7). Phthalates may also interfere with reproductive fitness in females, since production of estrogen is dependent upon production of testosterone precursors. Although fewer studies addressed the issue of female reproductive fitness compared to that of males, outcomes associated with phthalates exposure in women included interference with menstrual cycling (10), decreased number of follicles (eggs) (11), and early menopause (12).

There is an extensive animal toxicology literature documenting adverse effects on development of the reproductive organs of the male fetus as a result of the anti-androgenic effects of phthalates, including shortened anogenital distance in males. It is therefore not surprising that associations were observed between decreased anogenital distance and maternal phthalate exposure in several studies. Three studies in the U.S. (16,17,19) and a study in Sweden (15) reported associations between maternal phthalate levels and decreased anogenital distance, replicating a number of studies published before 2014. One U.S. study also reported an increased anogenital distance in girls (17). A study in Denmark, a population with very low phthalate exposure, reported a lack of association (14).

Several studies in the U.S found associations between a number of older phthalate metabolites and preterm birth (21-23), and a study in China found associations between preterm birth and 13 parent phthalates (24). One study in the U.S. (25) found both maternal and paternal exposure associated with intrauterine growth retardation. which is often a marker for later developmental problems. Studies in China also found association between a number of phthalates and intra-uterine growth retardation (26,28) and increased pregnancy loss (27). Changes in reproductive hormones in the mother or fetus were also reported to be associated with exposure to the older phthalate DEHP (18,20). Exploration of the potential mechanisms of poorer birth outcomes identified oxidative stress (29) and increased inflammation (30) as potential mechanisms. Other findings include decreased thyroid hormone levels (31,32) (critical for brain development) and increased blood pressure in pregnant women (33) linked to increased phthalate levels. A study in an occupationally-exposed population found an association between maternal exposure and heart defects (34).

The association between fetal exposure, and in some studies also exposure in childhood, was determined for a number of outcome categories (Table 4). Several studies observed deficits in neuropsychological function related to fetal exposure (37,40), including two in the U.S. reporting associations with DiNP or DiBP (35,36). A study in Taiwan assessing older phthalates found no associations with fetal exposure, but did find an association between concurrent exposure and adverse outcomes at 2-12 years (38). Adverse outcomes in these studies included deficits in IQ, processing speed, reasoning, memory, and verbal comprehension, as well as increased delinquent and aggressive behavior, and oppositional and conduct problems. Boys appeared to be more affected than girls on measures of antisocial behavior. A study in Spain found better performance on some measures associated with DEHP, but results were not stratified by sex (39). Recent expert reviews concluded that there is evidence that developmental exposure to phthalates results in developmental neurotoxicity in humans (Ejaredar et al., 2015; Miodovnik et al., 2014).

Associations were observed between fetal or childhood exposure and sexual development at puberty in several prospective studies (41-44). Effects include markers if early puberty, decreased uterine size and bone age in girls, and decreased testosterone in boys related to fetal exposure. Concurrent phthalate levels in the child were related to decreased testosterone levels in boys, and increased progesterone and FSH levels in girls (markers of puberty).

The potential relationship between phthalate exposure and body size is inconsistent, but may be sexually dimorphic (i.e., different in boys and girls) (45-48). There is also evidence for a link between increased exposure to phthalates during fetal development and wheezing, asthma, food allergy, or atopic dermatitis (49-53).

A number of studies assessed the association between the child's concurrent exposure and adverse outcomes (Table 5). Several studies reported changes in sex hormones and timing of puberty related to exposure to several phthalates, including newer ones, with some evidence of differential effects on boys and girls (54-57). Four studies reported an association between phthalate exposure and obesity, which also appeared to be sexually dimorphic (57-60). There is some evidence that concurrent levels of phthalates may result in an increased allergic response (61,62). A study using the U.S. NHANES database of over 1300 children reported an increase in systolic blood pressure associated with older and newer phthalates (63). Also taking advantage of the large NHANES database, an association between several phthalates and an increase in attention deficit disorder (ADD) or ADD plus learning disabilities was observed in a study of 1500 children (65). A study of children with or without attention deficit hyperactivity disorder (ADHD) reported higher levels of phthalates in cases than controls for boys, as well as poorer performance on a number of tests in ADHD children associated with increased phthalate levels (64). The thickness of specific cortical brain areas was decreased as a function of increased phthalate levels in children with ADHD.

In summary, the consequences of environmental exposure to phthalates in human populations is a very active area of research, with 65 studies identified published in the past two years related to effects on reproduction and development alone. Phthalate exposure is linked to adverse effects on both male and female reproductive fitness. Effects on fetal development are also consistent with the anti-androgenic effects of phthalates; in addition, adverse associations on neuropsychological function, metabolic homeostasis, and immune function were also observed in a number of studies. The child's concurrent phthalate levels were associated with effects on sexual maturation, metabolic function, immune response, and neuropsychological behaviors. There is therefore mounting evidence that exposure to *ortho*- phthalates from environmental sources may result in adverse outcomes in a number of functional domains. Moreover, effects were related to older phthalates being phased out of production, as well as the newer phthalates being substituted in commerce for older phthalates.

Table 1. Parent phthalate compounds and metabolites assayed in human tissue in epidemiological studies

Parent	Abbreviation	Metabolites	Abbreviation (alternate)
Older phthalates, tissue levels generally decreasing* (except MMP)†			
di(2-ethylexyl)	DEHP	mono-2-ethylhexyl	MEHP
		mono-2-ethyl-5 hydrohexyl	MEHHP (5 OH-MEHP)
		mono-2-ethyl-5 oxyhexyl	MEOHP (5 oxo-MEHP)
		mono-2-ethyl-5 carboxypentyl	MECPP (5 cx-MEPP)
		mono-(2-carboxymethylhexyl)	MCMHP
di-n-butyl	DnBP	mono-n-butyl	MnBP
		mono-3 carboxylpropyl	MCPP (3OH-MnBP)
benzyl butyl	BBP	mono-benzyl	MBzP
		mono-n-butyl	MnBP
diethyl	DEP	monethyl	MEP
dimethyl	DMP	monomethyl	MMP
Newer phthalates, tissue levels generally increasing*			
di-iso-butyl	DiBP	mono-iso-butyl	MiBP
dicyclohexyl	DCHP	monocyclohexyl	MCHP
di-n-octyl	DnOP	mono-3 carboxylpropyl	MCPP (3OH-MnBP)
		mono-octyl	MnOP
di-iso decyl	DiDP	mono-carbonynonyl	MCNP
		mono-isodecyl	MiDP
di iso nonyl	DiNP	mono-carboxy octyl	MCOP (OH-MiNP)
		mono-isononyl	MiNP
		mono-oxo-iso-nonyl	MOiNP (7-oxo-MMeOP)
		mono-hydroxy-iso-nonyl	MHiNP (7-OH-MMeOP)
		mono-carboxy-iso-octyl	MCiOP (7 cx-MMeOP, oxo-MiNP)
Parent phthalates analyzed in one study in China			
dinonyl	DNP		
di-amyl = di-n-pentyl	DPP		
dihexyl	DnHP		
bis(2-butoxyethyl)	DBEP		
bis(2-ethoxy ethyl)	DEEP		
bis(2-methoxyethyl)	DMEP		
bis(4-methyl-2-pentyl)	BMPP		

*National Health and Nutrition Survey (NHANES), U.S. CDC
†MMP levels approximately stable for 2001-2010, years assessed by NHANES

Table 2. Adverse fertility outcomes associated with male or female exposure

	Outcome	Population Tested	Metabolites or Parent Compounds Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
1.	fecundity or time to pregnancy: concurrent exposure of men and women	US, 2005-2009, 501 couples	MCPP, MMP, MEP, MiBP, MnBP, MECPP, MCMHP mono-[(2-carboxymethyl) hexyl], MEOHP, MEHHP, MCHP, MBzP, MEHP, MiNP, MOP in the urine of men and women partners	↑ MMP, MnBP, MBzP in men: longer time to pregnancy and decreased fecundity	DMP, DnBP, BBP	Buck Louis et al 2014
2.	reproductive outcomes: concurrent male exposure	US, 2004-2012, 218 couples	MEP, MBP, MiBP, MBzP, MCPP, MCOP, MCNP, MEHP, MEHHP, MEOHP, MECPP in urine	↑ MCOP: ↓ implantation; ↑ MnBP, MCOP, MCPP: ↓ live births	DiNP, DnBP, DnOP	Dodge et al 2015
3.	semen quality: concurrent adult exposure	US, 1999-2001, 420 men	MEHP, MEHHP, MEHOP, MECPP, MnBP, MiBP, MCPP, MBzP, MEP in urine	↑ MBzP: ↓ sperm motility	BBP	Thurston et al 2016
4.	semen quality: concurrent adult exposure	China, 2013, 1040 men	MMP, MEP, MBP, MBzP, MEHP, MEHHP, MEOHP, MnOP in urine	↑ MMP: ↓ sperm concentrations and sperm count; ↑ MEHP: ↑ abnormal sperm heads	DMP, DEHP	Wang et al 2015a

	Outcome	Population Tested	Metabolites or Parent Compounds Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
5.	semen quality, reproductive hormones: concurrent adult exposure	China, 2013, 687 men	MMP, MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MnOP in semen	↑ MnBP, MEHP, MEHHP, MEOHP: ↓ semen volume; ↑ MBzP: abnormal morphology; ↑ MBzP, MEHP: ↓ sperm velocity	DEHP, BBP, DnBP	Wang et al 2016
6.	markers of male reproductive function: concurrent adult exposure	Greenland, Poland, Ukraine, 2002-2004, 602 men	four metabolites detected (MEHHP, MECPP, MHiNP, MOiCP) + other contaminants in blood	↑ DiNP metabolites: ↓ testosterone; ↑ DEHP metabolites: marker of poorer epididymal function	DEHP, DiNP	Lenters et al 2015
7.	biomarkers of reproductive function: adult men	Greenland, Poland, Ukraine, 2002-2004, 589 men	MEHHP, MEOHP, MECPP, MECPP, MCiOP, MOiNP, MHINP in urine	↑ DEHP or DiNP metabolites: ↓ testosterone; ↑ DiNP metabolites: ↓ serum hormone binding globulin; ↑ DEHP metabolites: ↓ sperm concentration, semen volume	DEHP, DiNP	Specht et al 2014
8.	infertility in men: concurrent adult exposure	China, 2008-2009, 107 cases, 94 controls	DEHP, DEP, BBP, DnBP, DnOP (parent compounds) in semen	all five phthalates higher in infertile men	DEHP, DEP, BBP, DnBP, DnOP	Wang et al 2015b
9.	reproductive hormones: concurrent male exposure	China, 2007, 232 men from industrialized areas	MnBP, MEP, MEHP, MBzP in urine	↑ MnBP: ↓ sperm concentration	DnBP	Han et al 2014

	Outcome	Population Tested	Metabolites or Parent Compounds Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
10.	reproductive hormones and outcomes: maternal exposure	US, 1982-1986, 221 women	MnBP, MEP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCNP, MCOP, MCPP, MiBP, BPA in urine	↑ MCOP or BPA: ↓ luteal phase length; no effect on follicular phase length, fecundity, early pregnancy loss	DiNP	Jukic et al 2016
11.	antral follicle count (ovarian follicles measured by ultrasound) in women seeking infertility care: concurrent adult exposure	US, 2004-2012, 215 women	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, ∑DEHP, MCPP, MCOP, MCNP in urine	↑ ∑DEHP and individual DEHP metabolites: ↓ antral follicles	DEHP	Messerlian et al 2016
12.	early menopause: concurrent adult exposure	US NHANES, 1999-2008, 31,575 women	111 endocrine disrupting chemicals in urine	↑ MEOHP and MEHHP: ↑ early menopause	DEHP	Grindler et al 2015
13.	time to pregnancy, retrospective questionnaire	Canada, 2008-2011, 1597 women	11 phthalate metabolites, BPA, triclosan	no effect in this retrospective study		Vélez et al 2015

* MCPP is a metabolite of both DnBP and DnOP. MnBP is a metabolite of both DnBP AND BBP. Therefore both parent compounds are listed when associations to these metabolites are observed.

Table 3. Adverse birth and pregnancy outcomes associated with maternal/fetal exposure

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
14.	anogenital distance in boys: fetal exposure	Denmark, 2010-2012 (low exposure), 273 infants 3 months old	MEP, MiBP, MnBP, MBzP, MEHP, MEOHP, MEHHP, MECHP, MiNP, MHiNP, ∑DEHP, ∑DiNP in maternal urine	no effect		Jensen et al 2016
15.	anogenital distance in boys: fetal exposure	Sweden, 2008-2009, 196 boys at 21 months	MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiNP, MOiNP, MCiOP, ∑DEHP, ∑DiNP in maternal urine	↑ DiNP metabolites: ↓ anogenital distance	DiNP	Bornehag et al 2015
16.	anogenital distance in both sexes and penile width at birth: fetal exposure	US, 2010-2012, 753 mother-infant pairs	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, ∑DEHP in maternal urine	↑ three DEHP metabolites: ↓ anogenital distance in males only	DEHP	Swan et al 2015
17.	human chorionic growth hormone (hCG) and anogenital distance: fetal exposure	US, 2010-2012, 541 mother-infant pairs	hCG in maternal serum, MnBP, MBzP, MEHP, MEP, MiBP, MCPP, MCNP, MCOP in maternal urine	↑ MnBP, MBzP, MCOP: ↑ hCG for female fetuses, ↓ hCG for males; ↑ hCG: ↑ anogenital distance in females, ↓ in males; ↑ MnBP, MBzP, MEHP: ↓ anogenital distance in males	DnBP, DEHP, DiNP, BBP	Adibi et al 2015

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
18.	reproductive hormones in fetal blood: fetal exposure	Japan, 2002-2005, 202 pregnant women	MEHP in cord blood	↑ MEHP: ↓ testosterone/estradiol, progesterone, secretory products of Sertoli and Leydig (testes) cells in males	DEHP	Araki et al 2014
19.	sex organ development: interaction of prenatal stress and phthalate exposure: fetal exposure	US, 2012-2012, 738 mother-infant pairs	MEHP, MEOHP, MEHHP, MECPP, ∑DEHP, MEP, MBzP, MnBP, MiBP, MCPP in 1st trimester urine	↑ DEHP in low stress group: ↓ anogenital distance in males; no effect in high-stress group or females	DEHP	Barrett et al 2016
20.	sex steroids associated with abnormal male anatomy: fetal exposure	Denmark, 1980-1996, 300 controls 75 hypospadias 270 cryptorchidisms	DEHP and DiNP metabolites: MECPP and MHiNP detected in amniotic fluid	↑ MECPP: Δ in testosterone and insulin-like factor 3; no effect on anatomical abnormalities	DEHP	Jensen et al 2015
21.	preterm birth: maternal and fetal exposure	US, 2006-2008, 130 cases, 352 controls	MEHP, MEHHP, MEOHP, MECPP, ∑DEHP, MBzP, MnBP, MiBP, MEP, MCPP in maternal urine	↑ MEHP, MECPP, ∑DEHP: ↑ preterm birth; ↑ MEHP, MEHHP, MECPP, ∑DEHP, MnBP, MCPP: ↑ spontaneous preterm birth	DEHP, DnBP, DnOP	Ferguson et al 2014a

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
22.	preterm birth: maternal and fetal exposure	US, 2006-2008 130 cases, 352 controls	MEHP, MEHHP, MEOHP, MECPP, ∑DEHP, MBzP, MnBP, MiBP, MEP, MCPP in maternal urine measured 4x during pregnancy	∑DEHP: ↑ preterm birth; ↑ MECPP, ∑DEHP, MBzP, MnBP at specific times in pregnancy: ↑ preterm birth, third trimester most sensitive	DEHP, DnBP, BBP, BBP at individual times during pregnancy	Ferguson et al 2014b
23.	preterm birth: maternal and fetal exposure	US, 72 women with high-risk pregnancies	MEHP, MMP, MEP, MnBP, MCHP, MEHHP, MEOHP, MnOP, MCNP, MiDP, BPA in maternal urine	↑ MEHHP, BPA: ↓ gestation in males, MEHHP greater effect	DEHP	Weinberger et al 2014
24.	preterm birth and growth parameters: maternal and fetal exposure	China, 2011-2012, 207 women	DMP, DEP, DMEP, DiBP, DBP, BMPP, DEEP, DPP, DnHP, BBP, DBEP, DCHP, DEHP, DnOP, DNP (parent compounds) in maternal urine	↑ each phthalate; ↓ gestational age in females; ↑ DMEP: ↓ birth weight after adjustment, other phthalates associated with other markers of body size; ↑ in each phthalate except BBP and DCHP: ↓ birth weight and length, also most associated with additional growth measurements	DMP, DEP, DMEP, DiBP, DBP, BMPP, DEEP, DPP, DnHP, BBP, DBEP, DCHP, DnOP, DNP, DEHP	Huang et al 2014

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
25.	preconception biomarkers and birth outcome: maternal and paternal exposure	US, 2005-2009, 233 infants	MMP, MEP, MBP, MiBP, MEHP, MEHHP, MEOHP, MECPP, MCMHP, MBzP, MCHP, MCPP, MNP in maternal and paternal urine before pregnancy (90% pregnant within 6 months after sampling)	↑ maternal MCMHP, MMP, MEP, MnOP, MEHP: ↓ birth weight; ↑ paternal MEHP: ↓ birth weight; ↑DMP, DEP, DEHP metabolites: ↓ birth length, head circumference	DEHP, DnOP, DMP, DEP	Smarr et al 2015
26.	intrauterine growth restriction: fetal exposure	China, dates not given, mother-infant pairs, 42 cases, 84 controls	MnBP, MMP, MEHP, MEOHP, MEHHP in third trimester urine	MMP, MEHHP, MEOHP, ∑DEHP: ↑ in cases than controls; ↑ MEHHP, MEOHP: ↓ fetal growth in all subjects; males more affected	DMP, DEHP	Zhao et al 2014
27.	clinical pregnancy loss: embryonic/fetal exposure	China, 2011-2014, 132 cases, 172 controls	MMP, MEP, MiBP, MnBP, MEHP in urine	↑ MEP, MiBP, MnBP: ↑ pregnancy loss	DEP, DiBP, DnBP, BBP	Mu et al 2015
28.	expression of genes in placenta associated with fetal growth and development: fetal exposure	China, 187 mother-infant pairs	DMP, DEP, BBP, DEHP, DNOP (i.e. parent compounds) in umbilical cord blood	↑ DEHP: ↓ birth weight and gestational age in male infants; ↑ DMP, DEHP, DEP: ↑ gene expression of several genes associated with growth and development	DEHP, DMP, DEP	Li et al 2016

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
29.	biomarkers of oxidative stress (which may result in adverse pregnancy outcome): maternal exposure	US, 2006-2008 130 cases, 352 controls	MEHP, MEHHP, MEOHP, MECPP, ∑DEHP, MBzP, MnBP, MiBP, MEP, MCPP in urine measured 4x during pregnancy	all metabolites: ↑ oxidative stress; strongest associations with MBzP, MnBP, MiBP	DnBP, BBP, DEHP, DiNP, DEP, DnOP	Ferguson et al 2015a
30.	biomarkers of inflammation during pregnancy: maternal exposure	US, 2006-2008 130 cases, 352 controls	MEHP, MEHHP, MEOHP, MECPP, ∑DEHP, MBzP, MnBP, MiBP, MEP, MCPP in urine measured 4x during pregnancy	↑ MCPP, MBzP: increased inflammation	BBP, DnOP, DnBP	Ferguson et al 2015b
31.	thyroid and sex hormones: maternal exposure	Puerto Rico, 2010-2012, 106 pregnant women	MEHP, MnBP, MEHHP, MEOHP, MECPP, MCPP, MCOP, MCNP, MBzP, MiBP, MEP in urine	↑ MCPP and MCOP: ↓ free T_3; ↑ MEP: ↓ progesterone; ↑ ∑DEHP: ↓ free T_4	DiNP, DEP, DEHP DnOP, DnBP	Johns et al 2015
32.	thyroid function: fetal exposure	Taiwan, 2009-2010, 148 mother-infant pairs	MEHP, MEHHP, MEOHP, MnBP, MiBP, MEP, MMP, MiNP, MBzP in cord blood	↑ MBzP in cord blood: ↓ serum TSH	BBP	Kuo et al 2015
33.	blood pressure during pregnancy: maternal exposure	US, 2003-2006 369 women	MEP, MBzP, MCPP, ∑DBP (MnBP+ MiBP), ∑DEHP (MEHP+ MEHHP+ MEOHP+MECHP) in maternal urine	↑ MBzP: ↑ diastolic BP	BBP	Werner et al 2015

	Outcome	Population Tested	Metabolites or Parent Compound Measured	Phthalates Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
34.	congenital heart defects and parental exposure: fetal exposure	China, 2012-2013, 761 cases, 609 controls, occupationally exposed	"phthalates" unspecified in urine	↑maternal phthalates: ↑ventricular septal defects, pulmonary valve stenosis, patent ductus arteriosis; ↑paternal phthalates: ↑ventricular septal defect	"phthalates"	Wang et al 2015c

* MCPP is a metabolite of both DnBP and DnOP. MnBP is a metabolite of both DnBP AND BBP. Therefore both parent compounds are listed when associations to these metabolites are observed.

Table 4. Adverse outcomes in children associated with fetal exposure

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
35.	IQ at 7 years: fetal exposure	US, 1998-2006, 328 mother-offspring pairs	MnBP, MBzP, MEHHP, MEHP, MEP, MiBP in maternal urine	↑ MnBP, MiBP: ↓ full-scale IQ and processing speed, perceptual reasoning, working memory; ↑ MiBP: ↓ verbal comprehension; ↑ MBzP; ↓ perceptual reasoning	DnBP, DiBP, BBP	Factor-Litvak et al 2014
36.	neurobehavioral development in 6-10 years old boys and girls: fetal exposure	US, 1999-2005, 153 mother-infant pairs	MEHP, MEHHP, MEOHP, MiBP, MnBP, MBzP, MEP in maternal urine	↑ MiBP: ↑ inattention, rule-breaking, aggression, conduct problems in boys; ↑ ∑DEHP: ↑ somatic problems in boys; ↑ MBzP: ↑ oppositional behavior and conduct problems in boys, ↓ anxiety in girls	DEHP, DiNP, BBP	Kobrosly et al 2014
37.	behavioral outcomes in 8-year-old children: fetal exposure	Taiwan, 2000-2009, 122 mother-child pairs	MMP, MEP, MnBP, MBzP, MEOHP, MEHHP, MEHP in maternal urine	↑ MnBP, MEOHP, MEHP: ↑ externalizing problems; ↑ MnBP, MEOHP: ↑ delinquent and aggressive behavior	DnBP, DEHP, BBP	Lien et al 2015

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
38.	cognitive function at 2-12 years of age: fetal and childhood exposure	Taiwan, 2001-2002, 73-110 children depending on age of testing at 2, 5, 8,11, years	MMP, MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, ∑DEHP in maternal and child's urine	no association with maternal levels; ↑ child's MEOHP and ∑DEHP: ↓ IQ across ages	DEHP	Huang et al 2015
39.	neuropsychological development at 1, 4 and 7 years: fetal exposure	Spain 2004-2006, 367 children	∑DEHP, MBzP, MEP, MiBP, MnBP	↑ MBzP: ↓ psychomotor score at 4 years; ↑ ∑DEHP: ↑ social competence and ↓ ADHD scores; ↑ MEP: ↓ inattention at 4 years	BBP DEHP better outcome, but results not stratified by sex	Gascon et al 2015b
40.	neuropsychological development: fetal exposure and concurrent exposure at 2 years	Poland, begun 2007, 165 mother-infant pairs	MEP, MiBP, MnBP, MEHP, MEHHP, MEOHP, MnOP, MCOP, MCiOP, MCPP in urine	↑ DEHP, MCPP, MEHHP, MEOHP, ∑DnBP, high MW: ↓ psychomotor development at 2 years; no effect of postnatal exposure	DEHP, DnBP, DnOP	Polanska et al 2014
41.	female sexual maturation: fetal and concurrent childhood exposure	Mexico, 1997-2004, 116 mothers, 129 children ages 8-13 years	BPA, MEP, MnBP, MiBP, MBzP, MCPP, MEHP, MEHHP, MEOHP, MECPP in urine, hormones in blood	↑ maternal MEHP and other DEHP metabolites: ↑ pubic hair development and hormones associated with andrenarche; ↑ maternal MBzP, MEP: ↑ testosterone; no relation with concurrent exposure; no effect of BPA	DEHP, BBP, DEP	Watkins et al 2014

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
42.	pubertal development: fetal exposure	China, 2001-2002, 133 children at 8 and 11 years old	MEHP, MEHHP, MEOHP, MnBP, MBzP, MMP, MEP in third trimester urine	↑ MEHP, ∑DEHP: ↓ uterine size; ↑ MBzP: ↓ bone age in girls	DEHP, BBP	Su et al 2014
43.	male sexual maturation: fetal and concurrent childhood exposure	Mexico, 1994-2004, mothers and 118 boys ages 8-14 years	BPA, MEP, MnBP, MiBP, MBzP, MCPP, MEHP, MEHHP, MEOHP, MECPP in urine, hormones in blood	↑ maternal MEOHP, MBzP, MnBP, MCPP: ↑ sex hormone binding globulin; ↑ concurrent MEHP, MEOHP, MEHHP, MECPP, MBzP, MCPP: ↓ testosterone, ↑ SHBG; ↑ concurrent MiBP: ↓ testosterone	DEHP, DiBP, BBP, DnBP, DnOP	Ferguson et al 2014c
44.	sex steroid levels and reproductive development: fetal and concurrent childhood exposure	Taiwan, 2001-2009, 180 children 8 years old	MEHP, MEOHP, MEHHP, ∑DEHP, MnBP, MBzP, MMP, MEP in urine of pregnant women and children	no association with maternal levels; ↑ MEHP, MBzP; ↑ progesterone in girls; ↑ MnBP, MBzP: ↑ FSH in girls	DEHP, BBP, DnBP	Su et al 2014
45.	BMI and overweight status: fetal exposure	US, 1998-2006, 707 children exposed prenatally, 3 birth cohorts	MEP, MnBP, MiBP, MCPP, MBzP, MEHP, MEHHP, MEOHP, MECPP in maternal urine	↑ MCPP: ↑ overweight status in boys; ∑DEHP, MEP: ↓ BMI in girls	DEHP, DEP, DnOP, DnBP	Buckley et al 2016

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
46.	body size in children ages 5 and 7: fetal exposure	US, 1998-2006, 326-330 offspring, depending on age of testing	MEHP, MEHHP, MEOHP, MECCP, MiBP, MnBP, MBzP, MEP, MCPP in maternal urine	↑ non-DEHP component: ↓ BMI, waist circumference, fat mass in boys; DEHP component: no effect	DiNP+DnBP+BBP+ DEP+DnOP	Maresca et al 2016
47.	childhood growth and blood pressure: fetal exposure	Spain, 2004-2006, 391 mother-infant pairs, children assessed at 6 months through 7 years	MBzP, MEHP, MEHHP, MEOHP, MECPP, MiBP, MnBP, ∑DEHP, ∑high MW, ∑low MW in maternal urine	↑ ∑HMW: ↓ weight gain at 6 months in boys, ↑ weight gain in girls; ↑ ∑HMW: ↓ BMI in boys at all ages and ↑ BMI in girls; ↑ ∑HMW: ↓ systolic BP in girls only	∑high MW (DEHP + BBP)	Valvi et al 2015
48.	metabolic measures of diabetes and metabolic syndrome: fetal and peripubertal exposure	Mexico, women recruited 1997-2004, 250 offspring tested at 8-14 years old	MEP, MnBP, MiBP, MBzP, MCPP, MEHP, MEHHP, MEOHP, MECPP, BPA in third trimester urine and children	↑ MBzP, MEP, MCPP, ∑DEHP, ∑DnBP: numerous changes in homeostasis, depending on sex and pubertal status	DEHP, DnBP, BBP, DEP, DnOP	Watkins et al 2016
49.	asthma: fetal or concurrent postnatal exposure at 2-8 years	Taiwan, 2000-2001, 171 children tested at 2, 5, 8 years old	∑DEHP, MEHP, MBzP, MnBP, MEP in maternal and child's urine	↑ maternal DEHP, MBzP; ↑ wheezing in boys; ↑ MEHP at 2 and 5 years; ↑ asthma in boys; ↑ MEP at 5 years; ↑ wheezing and asthma in boys	DEHP, DEP, BBP, DnBP	Ku et al 2015

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
50.	asthma in children 5-11 years: fetal exposure	US, 1998-2006, 300 pregnant women	MEHHP, MBzP, MnBP, MEP in maternal urine	↑ MBzP, MnBP: ↑ asthma and asthma-like symptoms	BBP, DnBP	Whyatt et al 2014
51.	IgE levels and atopic dematitis (AD): fetal and childhood exposure at 2 and 5 years	Taiwan, 2004, 161-192 mothers and children depending on age	MEP, MBP, MBzP, MEHP in urine	↑ MEHP at 2 years: ↑ IgE levels in boys; ↑ MBzP at 2 years: ↑ AD	DEHP, BBP	Wang et al 2014
52.	food allergy and eczema: fetal and childhood exposure	Poland, 2007-, pregnant mothers and children at 2 years old, 147 children tested	MEP, MiBP, MnBP, MCPP, MEHP, MEHHP, MEOHP, MCOP, MCiOP, MnOP in maternal and child urine	↑ maternal MBzP: ↑ food allergy	BBP	Stelmach et al 2015
53.	respiratory tract infection and allergy at 6 and 14 months and 4 and 7 years: fetal exposure	Spain, 2004-2008, 174-391 children depending on outcome	MBzP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MnBP in urine	↑ ∑DEHP: ↑ wheeze, chest infections, bronchitis; ↑ MBzP: ↑ chest infections; ↑ ∑DEHP, MBzP: ↑ asthma at 7 years	DEHP, BBP	Gascon et al 2015a

* MCPP is a metabolite of both DnBP and DnOP. MnBP is a metabolite of both DnBP AND BBP. Therefore both parent compounds are listed when associations to these metabolites are observed.

Table 5. Adverse outcomes associated with concurrent childhood exposure

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
54.	delayed growth and puberty: childhood exposure	China, 2013-2014, 8-15 year old boys, 57 cases, 110 controls	MBP, MnBP, MiBP, MMP, MEP, MEHP, MEOHP, MEHHP in urine	↑ MBP, MEP, ∑ phthalates: ↓ serum testosterone; MEP, MBP, MEHP, total phthalates: risk of Constitutional Delay of Growth and Puberty (CDGP) (↓ bone age, height, puberty)	DBP, DEP, DEHP, ∑DBP + DEP + DEHP + DiBP + DnBP	Xie et al 2015
55.	pubertal timing : concurrent childhood exposure	China, 2010, 503 children 7-14 years old	MnBP, MMP, MEP, MEHP, MEHHP, MEOHP, ∑DEHP in urine	↑ MnBP: ↓ testicular volume; ↑ MEHHP, MEOHP: ↓ pubic hair stage in boys; ↑ MEHP, MEHHP, MEOHP, ∑DEHP: ↑ breast stage in girls	DEHP, DnBP, BBP	Shi et al 2015
56.	serum testosterone: concurrent exposure in men, women, children	US NHANES, 2011-2012, men, women, children, 2208 individuals	∑DEHP (MEHP+ MEHHP+ MEOHP+ MECPP), MBzP, MBP, MiBP, MEP, MCPP, MCNP, MCOP, MiNP, MMP in urine	↑ DEHP metabolites: ↓ T boys 6-12 years; ↑ DEHP and DnBP metabolites men 40-60: ~↓ T; ↑ ∑DEHP, MBzP, MnBP, MiBP, MCPP, MCNP, MCOP each: ↓ T at one or more ages in females	DEHP, BBP, DnBP, DiDP, DiNP, DiBP, DnOP	Meeker and Ferguson 2014

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
57.	obesity, pubertal maturity: childhood exposure	Taiwan, 2012-2013, 270 6.5-15 year olds	MMP, MEP, MiBP, MnBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, nonylphenol in urine	↑ metabolites of DEP, DnBP, DiBP, DEHP: ↑ obesity; ↑ MMP: ↓ plutarch in boys	DEHP, DEP, DiBP, DnBP, BBP, DMP	Hou et al 2015
58.	obesity: concurrent childhood exposure	China, 2001, 493 children tested at 8-10 or 11-13 years	LMW (MnBP+ MMP+ MEP), MEHP, MEHHP, MEOH, ∑DEHP in urine	↑∑ LHW, MEP: ↑obesity in boys; ↑ MEHP, MEHHP, ∑DEHP: ↓ obesity in girls	DEP, DEHP, DnBP + DMP + DEP	Zhang et al, 2014
59.	obesity: concurrent exposure of children, adolescents, adults	US NHANES, 2007-2010	MnBP, MEP, MiBP, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCNP, MCOP	↑ low MW (MnBP + MEP + MiBP): ↑ obesity in male children and adolescents; ↑ high MW (MECPP + MEHHP + MEOHP + MEHP + MBzP + MCNP + MCOP): ↑ obesity in adults; ↑ ∑DEHP: ↑ obesity in female adults	DEHP, DnBP + DEP + DiBP, DEHP + BBP + DiDP + DiNP	Buser et al 2014
60.	adiposity and insulin insensitivity: concurrent childhood exposure	Italy, 41 obese, 31 control children, age 12 years	MEHP, MEHHP, MEOHP, MECPP, MCMHP in urine	↑ levels of MECPP and MEHHP in obese compared to controls; differences in DEHP metabolism depending on obesity, age, and pubertal status	DEHP	Smerieri et al, 2015

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
61.	atopic dermatitis (AD): concurrent childhood exposure	Korea, 2012, 224 cases, 224 controls ages 3-6 years	MEHHP, MEOHP in urine	↑ ∑DEHP: ~↑ AD at 3 years; non-monotonic function: ↓ risk at low and ↑ risk at high levels	DEHP	Choi et al 2014
62.	asthma, allergic rhinoconjuncitivitis, AD: concurrent childhood exposure	Denmark, 222 controls, 68-81 cases depending on outcome, children 3-5 years	MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP in urine	↑ MEP: ~↑ AD	DEP	Callesen et al 2014
63.	blood pressures and markers of lipid metabolism in children and adolescents: concurrent exposure	US NHANES, 2009-2012, 1329 children for BP, 367 for triglyceride, 4105 for HDL cholesterol	DEHP, DiNP, DiDP metabolites, low molectular weight (MEP + MnBP + MiBP + MMP), high molecular weight DEHP metabolites (MEHP + MEHHP + MEOHP + MECPP), high molecular weight non-DEHP metabolites (MBzP + MCPP + MCOP + MiNP + MCNP) in urine	↑ high molecular weight, DEHP, DiNP and DiDP metabolites: ↑ systolic BP; also association with individual high molecular weight metabolites	DEHP, DiNP, DiDP, total high molecular weight (DEHP + BBP DnOP + DiNP + DiDP)	Trasande and Attina 2015

	Outcome	Population Tested	Metabolites Measured	Metabolites Associated With Adverse Outcomes	Parent Phthalates* Associated with Adverse Outcomes	Reference
64.	externalizing behavior and brain cortical thickness: childhood exposure	Korea, 180 children 6-15 years with ADHD, 438 controls	MBP, MEHP, MEOHP in urine	↑ MEHP, MEOHP, MBP: ↑ in cases than controls; ↑ ∑DEHP: ↓ cortical thickness; ↑ DEHP and DEP metabolites: poorer performance in children with ADHD on Clinical Global Impression, Disruptive Behavior Disorder Rating Scale; ↑ MBP: ↑ aggression and externalizing behavior in ADHD children; ↑ DEHP: increased impulsivity on test	DBP, DEHP	Park et al 2015
65.	attention deficit disorder, learning disabilities, or ADD + LD: childhood and adolescent exposure	US NHANES, 2001-2004, 1493 children 6-15 years old	∑DEHP(MEHP+MEHHP+ MEOHP), ∑DnBP (MnBP+ MiBP), ∑DnOP (MCPP+MOP), MBzP, MEP MiNP, MMP in urine	↑ ∑DEHP and high MW: ↑ ADD; ↑ ∑DEHP, ∑DBP and high MW ~ ↑ ADD plus LD in girls (HMW = MBzP + MCPP + MEHP + MEHHP + MEOHP)	DEHP, DBP, BBP + DnOP + DEHP + DnBP	Chopra et al 2014

* MCPP is a metabolite of both DnBP and DnOP. MnBP is a metabolite of both DnBP AND BBP. Therefore both parent compounds are listed when associations to these metabolites are observed.

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