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Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence

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Abstract

Objective: We performed a systematic review of the epidemiology literature to identify the male reproductive effects associated with phthalate exposure.

Data sources and study eligibility criteria: Six phthalates were included in the review: di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), butyl benzyl phthalate (BBP), and diethyl phthalate (DEP). The initial literature search (of PubMed, Web of Science, and Toxline) included all studies of male reproductive effects in humans, and outcomes were selected for full systematic review based on data availability.

Study evaluation and synthesis methods: For each outcome, studies were evaluated using criteria defined a priori for risk of bias and sensitivity by two reviewers using a domain-based approach. Evidence was synthesized by outcome and phthalate and strength of evidence was summarized using a structured framework.

Results: The primary outcomes reviewed here are (number of included/excluded studies in parentheses): anogenital distance (6/1), semen parameters (15/9), time to pregnancy (3/5), testosterone (13/8), timing of pubertal development (5/15), and hypospadias/cryptorchidism (4/10). Looking at the overall hazard, there was robust evidence of an association between DEHP and DBP exposure and male reproductive outcomes; this was based primarily on studies of anogenital distance, semen parameters, and testosterone for DEHP and semen parameters and time to pregnancy for DBP. There was moderate evidence of an association between DINP and BBP exposure and male reproductive outcomes based on testosterone and semen parameters for DINP and semen parameters and time to pregnancy for BBP. DIBP and DEP were considered to have slight evidence of an association. For DIBP, the less conclusive evidence was attributed to a more limited literature base (i.e., fewer studies) and lower exposure levels in the population, decreasing

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Appendix A. Supplemental materials
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the ability to observe an effect. For DEP, the findings were consistent with experimental animal data that suggest DEP does not haves as strong an anti-androgenic effect as other phthalates.

Conclusions and implications of key findings: Overall, despite some inconsistencies across phthalates in the specific outcomes associated with exposure, these results support that phthalate exposure at levels seen in human populations may have male reproductive effects, particularly DEHP and DBP. The relative strength of the evidence reflects differing levels of toxicity as well as differences in the range of exposures studied and the number of available studies.

The views expressed are those of the authors and do not necessarily represent the views or policies of the U.S. EPA.

1. Introduction

Phthalic acid diesters (phthalates) are a class of manmade and multifunction chemicals used in a wide array of consumer and industrial products, including as plasticizers in polyvinyl chloride plastics, excipients in some medications, and scent retainers in some personal care products. Human exposure is ubiquitous across the lifespan, including in utero through maternal exposures. Ingestion, inhalation, and dermal contacts are also routes of exposure for the general population (Johns et al., 2015). After exposure, phthalate diesters are rapidly metabolized to monoester metabolites and excreted in the urine. The group of phthalates encompasses a variety of compounds with different structures, properties, and use. The phthalates, that are the focus of this paper are: di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), butyl benzyl phthalate (BBP), and diethyl phthalate (DEP). Within this group, there are phthalates that are structurally similar and moderately correlated based on human biomonitoring data (e.g., DBP and DiBP). Other are phthalates differ considerably (e.g., long vs short chain; DEP and DEHP); correlations between these phthalates are typically low (Johns et al., 2015).

Phthalates have well documented anti-androgenic activity in rodent studies resulting in reduced circulating testosterone and male reproductive tract abnormalities (Johnson et al., 2012; Howdeshell et al., 2008). Individual studies and reviews in humans and animals, including a recent report from the National Academies of Science (National Academies of Sciences, Engineering, and Medicine, 2017), have investigated male reproductive effects of phthalate exposure, but have not looked across the full spectrum of male reproductive effects (i.e., from exposures and outcomes during different lifestages, including fetal development, infancy, childhood, puberty, and sexually mature life-stages) in epidemiological studies for DEHP, DINP, DBP, DIBP, BBP, and DEP. Five of the selected phthalates (DEHP, DINP, DBP, DIBP, and BBP) were chosen because they are the most potent with respect to producing the “phthalate syndrome” of male reproductive effects in rats (National Research Council, 2008)and their metabolites have been frequently observed in human populations studies; DEP is not one of the “phthalate syndrome” compounds but was included because it is often the phthalate to which humans have the highest exposure.

We performed a systematic review of the epidemiology literature with the goal of evaluating the strength of evidence of the association between phthalate exposure and male reproductive effects, including the following outcomes: anogenital distance, semen parameters, time to pregnancy (male exposure), testosterone, timing of pubertal development, and hypospadias/cryptorchidism. The human health relevance of these outcomes is summarized briefly in Table 1. These outcomes include a variety of measures relevant to different life-stages: anogenital distance and hypospadias/cryptorchidism may reflect exposure or responsiveness to testosterone during fetal development, pubertal development depends on the functioning of multiple hormonal pathways, and semen parameters and time to pregnancy, measured in adults, are indicators of fertility. Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, has been estimated to affect 15% of couples, and male-related factors are implicated in approximately 20–50% of these cases (Agarwal et al., 2015).

2. Methods

2.1. Literature search and screening

The literature search and screening, study evaluation, data extraction, and evidence synthesis methods are described in detail in the systematic review protocol (Supplemental materials, Section 3). Briefly, epidemiology studies were identified by conducting a single broad literature search on all six phthalates of interest (DEHP, DINP, DBP, DIBP, BBP, DEP) and all outcomes. The Population, Exposure, Comparators, and Outcome (PECO) are available in the protocol (Section 2). The following databases were searched: PubMed, Web of Science, and Toxline, initially in 2013, with updates every 6–12 months through January 2017. Forward and backward searches were also performed. Title/abstract and full text screening was performed by two reviewers.

2.2. Study evaluation

Studies were evaluated by at least two reviewers using uniform approaches for each group of similar studies. Key concerns were risk of bias (factors that affect the magnitude or direction of effect) and insensitivity (factors that limit the ability of a study to detect a true effect) (Cooper et al., 2016). Evaluation was conducted for the following domains: exposure measurement, outcome ascertainment, participant selection, confounding, analysis, sensitivity, and selective reporting. Phthalate and outcome-specific criteria were developed prior to evaluation. For exposure, most of the available studies relied on phthalate metabolite biomarkers (a list of metabolites for each phthalate is provided in the protocol, Section 1.3). Different criteria were developed for short-chain (DEP, DBP, DIBP, BBP) and long-chain (DEHP, DINP) phthalates due to better reliability of single measures for short-chain phthalates. Measurement in urine was considered to be the best proxy of exposure (Johns et al., 2015). Biomarker measures based on samples other than urine (e.g., blood, amniotic fluid, breast milk) were considered to be critically deficient for all short-chain phthalates and for primary metabolites (e.g., MEHP, MINP) of long-chain phthalates (Johns et al., 2015). Rationale for these criteria and additional details for all domains are available in the protocol (Section 4.1.1) and an abbreviated version is available in the key methods supplement. For each study, in each evaluation domain, reviewers reached a consensus

rating regarding the utility of the study for hazard identification, with categories of *Good*, *Adequate*, *Deficient*, or *Critically deficient*. These ratings were then combined to reach an overall study confidence classification of *High*, *Medium*, *Low*, or *Uninformative*. Studies were evaluated for their suitability for each outcome investigated, and could receive different ratings for each outcome. Descriptions of each of the categories can be found in the protocol in supplemental materials (Section 4) and the key methods supplement. Study evaluations were documented in Health Assessment Workspace (HAWC), and ratings and rationale are publicly available.

2.3. Evidence synthesis

After study evaluation, the evidence for each outcome was synthesized separately for each phthalate, using the following aspects of an association that may suggest causation: consistency, exposure-response relationship, strength of association, temporal relationship, biological plausibility, and coherence. Based on this synthesis, the evidence was assigned a strength of evidence conclusion of *Robust*, *Moderate*, *Slight*, *Indeterminate*, or *Compelling evidence of no effect*. *Robust* and *Moderate* describe evidence that supports a hazard, differentiated by the quantity and quality of information available to rule out alternative explanations for the results. *Slight* and *Indeterminate* describe evidence that could support a hazard, or could support the absence of a hazard. These categories are generally limited in terms of quantity or confidence level of studies, and serve to encourage additional research across the exposure range experienced by humans. *Compelling evidence of no effect* requires several high confidence studies with consistent null results. The ratings for the individual outcomes were then summarized into an overall conclusion for male reproductive effects by phthalates, using a structured framework available in the key methods supplement and the protocol (Section 6). No statistical quantitative meta-analysis was performed due to substantial differences across studies.

3. Results

An abbreviated version of the literature flow diagram is shown in Fig. 1. Full results of the literature search and screen are described in Supplemental materials. For each outcome, the studies included and excluded based on study evaluation are described in the respective section.

3.1. Anogenital distance

3.1.1. Study selection and evaluation—Based on the exposure evaluation strategy described in the protocol (Section 4.1.1), one study (Huang et al., 2009) was excluded because it was based on the measurement of phthalate metabolites in amniotic fluid. The specific phthalate metabolites examined in the remaining seven papers (describing six studies) and the study evaluations are summarized in Table 2 and full rationale are available at https://hawcprd.epa.gov/summary/visual/100000001/.

All included studies are birth cohorts, varying in size between 73 and 738 mother-child pairs in the analysis sample. All but one were limited to male offspring; (Swan et al., 2015) included both male and female offspring and stratified the analysis by sex. All of the studies

were downgraded for exposure assessment as exposure was based on a single spot urine sample. The timing of collection (1st, 2nd, or 3rd trimester) varied among the studies; this variability was not considered to be a basis for downgrading the confidence in the results because the correlation in measures across trimesters is relatively high (Johns et al., 2015). The (Bustamante-Montes et al., 2013) analysis was limited by the fact that MBP, MBzP, and MEP were detected in ≤10% of samples, which is inconsistent with results of biomonitoring studies globally. The corresponding reduction in sensitivity contributed to the overall *low confidence* rating of this study. Limitations of the (Swan, 2008) paper (an extension of the initial study on this topic published by Swan et al., 2015) include a wide age range (1–36 months) and lack of information on the measurement evaluation strategy and standardization and reliability of measures across the different centers. Three studies were classified as *medium confidence* (Bornehag et al., 2015; Swan et al., 2015; Jensen et al., 2016), and the remaining three were classified as *low confidence*.

3.1.2. Results—Fig. 2 provides a comparison of regression coefficients (plotted against the median of exposure for each study) for the three *medium confidence* studies (Bornehag et al., 2015; Swan et al., 2015; Jensen et al., 2016). Because some of the studies used a natural logarithm (ln) transformation of the phthalate metabolite variables and others used a log10 transformation, the regression coefficients in Swan et al., 2015 and Swan, 2008 with log10 transformations were recalculated (divided by ln10) to make the results directly comparable. Fig. 2 also summarizes in tabular format results (recalculated if applicable) from all studies with the relevant metabolite, including *low confidence* studies.

Evaluation of the evidence for an association between exposure to DEHP and AGD is based on six studies (Fig. 2A). The study with the highest exposure levels for the sum of DEHP metabolites (Bornehag et al., 2015) reported the strongest negative association between DEHP exposure and AGD, and the study with the lowest exposure levels (Jensen et al., 2016) reported the weakest association of the three *medium confidence* studies. (Swan et al., 2015) and (Swan, 2008) also reported statistically significant negative associations with sum DEHP (Swan et al., 2015) and MEHP (Swan, 2008; Swan et al., 2015). Given the consistency across medium confidence studies, evidence of a relationship between AGD and DEHP exposure is considered *moderate*.

Three studies (Bornehag et al., 2015; Swan et al., 2015; Jensen et al., 2016) investigated the association between DINP exposure and AGD (Fig. 2B). (Bornehag et al., 2015), a *medium confidence* study, reported a statistically significant association between shorter AGD with increasing DINP exposure (summed metabolites), while the other two *medium confidence* studies (Swan et al., 2015; Jensen et al., 2016) reported no association between DINP exposure and AGD. The association was observed in the study with the highest exposure levels, which is consistent with a dose response; however, due to the limited number and lack of consistency in the other studies, this evidence is considered *slight*.

The same five studies presented results on the association between DBP (measured by MBP) exposure and AGD (Fig. 2C). (Bornehag et al., 2015) again reported the strongest inverse association between AGD and DBP exposure and the highest exposure levels of MBP in this group of studies. Both (Swan et al., 2015) and (Swan, 2008) also reported

inverse associations, with the latter being statistically significant. The remaining two studies reported no association. This evidence is considered *moderate*.

Three studies (Swan et al., 2015; Jensen et al., 2016; Swan, 2008) that examined the association between DIBP (measured by MIBP) and AGD were available (Fig. 2D). (Swan, 2008), a *low confidence* study, and Swan et al., 2015, a *medium confidence* study reported inverse associations, but neither were statistically significant, and the effect size in the latter study was small. The other *medium confidence* study, with higher exposure levels, reported no association. The low exposure levels in all three studies may have decreased sensitivity. This evidence is considered *slight*.

Five studies (Bornehag et al., 2015; Swan et al., 2015; Jensen et al., 2016; Swan, 2008; (Suzuki et al., 2012) presented results on the association between BBP (measured by MBzP) (Fig. 2E) exposure and AGD. Among three *medium confidence* studies, (Bornehag et al., 2015) and (Jensen et al., 2016) reported inverse associations, though neither was statistically significant; the larger effect estimate was seen in the study with higher exposure levels. (Swan et al., 2015) and the two *low confidence* studies (Suzuki et al., 2012; Swan, 2008) reported no association. This evidence is considered *slight*.

Five studies (Bornehag et al., 2015; Swan et al., 2015: Jensen et al., 2016; Swan, 2008; Suzuki et al., 2012) reported on the association between DEP exposure (measured by MEP) and AGD (Fig. 2E). In the three *medium confidence* studies, there was no evidence of an association. In addition, discordant results (i.e., one positive association and one inverse association) were observed in AGD_{AS} and AGD_{AP} (two different AGD measurements) in both (Jensen et al., 2016) and (Bornehag et al., 2015) (AGD_{AS} result in figure, AGD_{AP} results: Jensen et al., 2016): $\beta = 0.02$ (−0.54,0.58); (Bornehag et al., 2015): $\beta = -1.30$ (−3.40,0.81)). Since there is no evidence at this time that one of these AGD measures is a more sensitive measure of response to phthalate exposure, these study findings are considered inconsistent. One *low confidence* study, (Swan, 2008), reported a statistically significant inverse association between MEP and AGD. Overall, evidence is considered *slight*.

In summary, there is *moderate* evidence of an inverse association between AGD and exposure to DEHP and DBP, with mostly consistent results reported among the studies. Evidence for DINP, BBP, DIBP, and DEP is *slight*. The weaker evidence of an association for the DINP, BBP, and DIBP may be due to a combination of low exposure levels (i.e., poor sensitivity) and data availability (i.e., fewer available studies). While evidence for DEP was also rated *slight*, there were high exposure levels, so the relative lack of evidence of an association is consistent with experimental animal data that suggest that this phthalate does not have as strong an anti-androgenic effect as other phthalates. Additional studies, with higher confidence ratings, would be needed to draw a firm conclusion that DEP was not associated with AGD in humans.

3.2. Testosterone in infants

Testosterone plays an important role in the development of the male reproductive system and is therefore an important link between phthalates and other outcomes in this section,

such as anogenital distance, hypospadias and cryptorchidism. Three studies (four papers) (Main et al., 2006) (Araki et al., 2016; Araki et al., 2014; Lin et al., 2011) examined the relationship between prenatal phthalate exposure and testosterone levels in newborn boys. Two studies (Main et al., 2006; Araki et al., 2014; Araki et al., 2016) were excluded due to the measurement of exposure in breast milk, blood, and cord blood, respectively, as described in the exposure evaluation strategy (see protocol Section 4.1.1). The remaining *low confidence* study (Lin et al., 2011) was a pregnancy cohort, with phthalate exposure measured in a single spot urine sample during the third trimester, and reproductive hormones measured in cord blood using appropriate methods. Among 81 male newborns, there was no association (Pearson's correlation coefficients for free testosterone: MEP-0.10, MBP-0.11, MBzP 0.05, ∑DEHP 0.06, *p*-values for all > 0.1). This evidence is considered *indeterminate*.

3.3. Semen parameters

3.3.1. Study selection and evaluation—Based on the exposure evaluation, nine of the 28 epidemiology papers (Table 3) identified in the search with data on sperm parameters and exposure in adults were excluded because they used measurements of phthalates in tissues other than urine (i.e., blood or semen) or because of other critical deficiencies in methodology or reporting of results. The specific phthalates examined in the remaining 15 studies (19 papers) and their evaluations are summarized in Table 3 (Joensen et al., 2012; Kranvogl et al., 2014; Lenters et al., 2014; Pan et al., 2011, 2016; Pant et al., 2008, 2014; Toshima et al., 2012; Zhang et al., 2006). Full rationale are available at https://hawcprd.epa.gov/summary/visual/100000065/.

Outcome-specific criteria for study evaluation are available in the supplement. Population-based studies were preferred, but clinic or center-based samples were also acceptable as long as they were not limited to volunteers with known male fertility issues. Most of the studies are cross-sectional, varying in size between 45 and 1066 adult males. In most studies, a single urine sample was collected concurrent with outcome assessment (semen analysis). Exceptions are (Liu et al., 2012) and (Wang et al., 2015a, 2015b, 2015c), which had two urine samples several days apart and the same day, respectively. Because the relevant time window of exposure for sperm production was considered to be relatively short (< 90 days), concurrent measurement was not considered a limitation for this outcome. (Specht et al., 2014) used blood samples which were acceptable for secondary metabolites of DEHP and DINP, and (Huang et al., 2011), in which personal air samples were collected during a work shift. All of the studies assessed exposure in adulthood; one study (Axelsson et al., 2015b) additionally examined prenatal exposure, which is considered separately. Thirteen studies were classified as *medium confidence*, and two as *low confidence* (Den Hond et al., 2015, 3,045,496; Herr et al., 2009).

3.3.2. Results—Comparing results across studies is challenging due to the wide variety of analysis methods used. It is important to carefully consider the interpretation of the type of coefficient when comparing across results: for example, results supporting an association between increasing exposure and poorer semen quality will be reflected by a negative coefficient when the outcome is modeled as a continuous variable, and as a positive coefficient when the outcome is modeled as the probability of an unfavorable outcome (e.g.,

prevalence of sperm concentration < 15×10^6 per ml). To facilitate comparisons, the sets of studies reporting each type of metabolite in Table 4 are grouped by type of effect estimate (Beta or OR), and further sorted by overall confidence rating. Studies using dichotomous outcomes (and OR estimates) used World Health Organization guidelines for establishing cutoffs, with all using the 1999 version, with the exception of Wang et al. (2015a, 2015b, 2015c), which used the 2010 version. Both versions are similar in establishing abnormal semen quality (Catanzariti et al., 2013).

Evaluation of the evidence for an association between exposure to DEHP and sperm parameters is based on 14 studies. Results for summed DEHP metabolites were used when available; if not available, results for MEOHP or MEHP were used (Table 4). An inverse relationship (decreased semen quality with increased DEHP exposure as measured by metabolite levels) was observed for sperm concentration in seven studies, and for motility in four studies. However, of all of the findings, only one for sperm concentration (Bloom et al., 2015) and two for motility (one for MEOHP and one for MEHP) (Axelsson et al., 2015a; Jurewicz et al., 2013) were statistically significant, and there was no indication that studies with higher median exposure levels were more likely to observe an association. The inverse findings were also supported by data (not reviewed systematically) from studies that indicated increased apoptosis (Huang et al., 2014); (Wang et al., 2016b; You et al., 2015), increased reactive oxygen species (ROS) generation (Huang et al., 2014), and increased sperm aneuploidy (Jurewicz et al., 2013)with increasing DEHP exposure, which may help inform potential mechanisms of action. Overall, there is *moderate* evidence of an association between increased DEHP and decreased semen quality, particularly for sperm concentration.

Four *medium confidence* studies examined the association between DINP exposure (measured by MCiOP or MINP) and semen parameters (Table 5). All three studies that looked at morphology (Axelsson et al., 2015a; Pan et al., 2015; Jurewicz et al., 2013) reported an inverse association between exposure and sperm quality, two of the three that looked at motility also reported an association (Axelsson et al., 2015a; Pan et al., 2015), and two of four studies reported an association with concentration (Specht et al., 2014) (Pan et al., 2015), including one with an exposure-response gradient (Specht et al., 2014). However, the only finding that was statistically significant was for morphology in Jurewicz et al. (2013). Given the consistency across studies for morphology, the relationship between DINP exposure and sperm parameters is considered *moderate*.

Twelve studies reported results on the association between DBP exposure (measured by MBP) and semen parameters (Table 6). Eight studies reported decreased concentration with increasing DBP exposure, with statistically significant and monotonic dose-response relationships observed in three (Wang et al., 2015b; Liu et al., 2012; Hauser et al., 2006). These findings were observed across the range of exposures observed in the studies. Seven studies supported an association for motility, including two that were statistically significant (Axelsson et al., 2015a; Hauser et al., 2006), but studies with lower exposure levels were more likely to report an association than studies with higher levels. Of the ten studies that included an evaluation of morphology, six support an association. Evidence for effects on semen were also supported by data (not reviewed systematically) from a study that indicated increased sperm aneuploidy with increased DBP exposure (Jurewicz et al., 2013),

which may help inform potential mechanisms of action. No association was observed between DBP exposure and sperm apoptosis in one study (Wang et al., 2016b; You et al., 2015). Overall, due to the consistency across several *medium confidence* studies and the observation of dose-response relationships, evidence of an association between increased DBP exposure and decreased semen quality, specifically sperm concentration, is considered *robust*.

Four studies reported results for DIBP exposure (measured by MIBP) and semen parameters (Table 7). Two *medium confidence* studies (Bloom et al., 2015) reported associations between increasing MIBP concentrations and one or more measures of decreased semen quality. The remaining *medium* confidence (Thurston et al., 2016) and *low* confidence (Den Hond et al., 2015) studies reported no association. Given the limited data and lack of consistency, the relationship between DIBP exposure and semen parameters is considered *slight*.

Ten studies reported results on the association between BBP exposure (measured by MBzP) and semen parameters (Table 8). Four studies that examined sperm concentration and eight studies that examined motility reported an association between increased BBP exposure and decreased sperm quality; for motility, studies with higher exposure levels were more likely to find an association. Statistically significant associations were reported with sperm concentration in two studies (Bloom et al., 2015) (Pan et al., 2015); and with motility in one study (Thurston et al., 2016). Only two studies examining morphology reported an association. Evidence for effects on semen were also supported by data (not reviewed systematically) from a study that reported increased sperm aneuploidy with increased BBP exposure (Jurewicz et al., 2013), which may help inform potential mechanisms of action. No association was observed between BBP exposure and sperm apoptosis in one study (Wang et al., 2016b; You et al., 2015). Overall, due to associations being reported in several *medium confidence* studies, there is *moderate* evidence that BBP exposure is associated with decreased sperm quality, specifically motility.

Twelve studies investigated the association between DEP exposure (measured by MEP) and sperm parameters (Table 9). An inverse relationship (decreased semen quality with increased DEP exposure as measured by metabolite levels) was observed for sperm concentration in four studies, for motility in two studies, and for morphology in three studies. No association, or a positive association, was observed in the remaining studies. Given the lack of consistency across studies despite high exposure levels, this evidence is considered *indeterminate*; additional high confidence studies, at high exposure levels, would be needed to conclude there was compelling evidence of no effect.

In summary, there is *moderate* to *robust* evidence of an association between DBP, BBP, DEHP, and DINP exposure and sperm parameters, *slight* evidence for DIBP, and *indeterminate* evidence for DEP. The strongest evidence was observed for sperm concentration, while evidence for motility and morphology was more limited (with the exception of BBP and DINP, respectively). There were notably fewer studies of DIBP, which may explain the lack of an association. DEP had both a reasonable number of studies and

high exposure levels without a clear association; these results support differences in DEP's potency or activity relative to other phthalates.

3.4. Time to pregnancy (male exposure)

3.4.1. Study selection—Three studies looked at male exposure to phthalates and its association with time to pregnancy. Two were excluded because the exposure was measured after the outcome (Table 10) (Modigh et al., 2002; Specht et al., 2015). The specific phthalates examined in the remaining study are summarized in Table 10. This was a prospective cohort identified through population-based sampling. Based on the criteria described in the outcome-specific criteria (supplement), it was classified as *high confidence*, and the rationale for domain ratings are available at https://hawcprd.epa.gov/rob/study/100000037/.

3.4.2. Results—In Buck Louis et al. (2014), for DBP and BBP (measured by MBP and MBzP, respectively), there were statistically significant associations between increased exposure and increased time to pregnancy, or decreased fecundity (Table 11). Because the study is high confidence and because of the coherence with semen parameters, this evidence is considered *moderate*. For DEHP and DIBP, there was some evidence that increased exposure to these phthalates is associated with increased time to pregnancy, but the results were not statistically significant, and this evidence is considered *slight*. For DEP and DINP, no association was reported; given the limited number of studies and for DINP, the relatively low range of exposures, the evidence is considered *indeterminate*.

3.5. Testosterone

3.5.1. Study selection and evaluation—Based on the exposure evaluation criteria, eight of the 21 epidemiology papers (Table 12) identified in the search with data on testosterone were excluded because they used measurements in tissues other than urine (i.e., blood or semen), did not report results for individual metabolites, or did not discuss collection time of outcome sample. The specific phthalates examined in the remaining 13 studies (15 papers) and study evaluations are summarized in Table 12 (Fong et al., 2015; Janjua et al., 2007; Lenters et al., 2014; Li et al., 2011; Pan et al., 2016; Xu et al., 2015). Full rationale for ratings are available at https://hawcprd.epa.gov/summary/visual/100000066/, and outcome-specific criteria are available in the supplement. All of the studies are cross-sectional, varying in sample size between 25 and 1066 adult men in analysis. As with studies of sperm parameters, cross-sectional design with concurrent measurement of exposure and outcome (testosterone concentration) was not considered a limitation. In most studies, a single urine sample was collected concurrent with outcome assessment, with the exception of Wang et al. (2015c), which had two same-day urine samples, and Specht et al. (2014), in which blood samples were used for secondary metabolites of DEHP and DINP. Testosterone was the most studied of the relevant reproductive hormones, and was therefore the focus of this review.

Nine studies (ten papers) were classified as *medium confidence* (Axelsson et al., 2015a; Axelsson et al., 2015b; Pan et al., 2015; Han et al., 2014; Meeker and Ferguson, 2014; Specht et al., 2014; Jurewicz et al., 2013; Mendiola et al., 2011; Meeker et al., 2009);, and

four studies were classified as *low confidence* (Chang et al., 2015; Den Hond et al., 2015; Park et al., 2010; Pan et al., 2006).

3.5.2. Results—Evaluation of the association between exposure to DEHP and testosterone is based on 13 studies (Axelsson et al., 2015a; Chang et al., 2015; Den Hond et al., 2015; Pan et al., 2015; Wang et al., 2015c; Han et al., 2014; Meeker and Ferguson, 2014; Specht et al., 2014; Jurewicz et al., 2013; Mendiola et al., 2011; Park et al., 2010; Meeker et al., 2009; Pan et al., 2006). Results for summed DEHP metabolites were used when available; if not available, results for MEOHP (preferred) or MEHP were used. Eight studies (Axelsson et al., 2015a; Wang et al., 2015c; Meeker and Ferguson, 2014; Specht et al., 2014; Jurewicz et al., 2013; Park et al., 2010; Meeker et al., 2009); (Pan et al., 2015); reported decreased testosterone levels with higher DEHP exposure (Table 13), including findings from two studies that were statistically significant (Specht et al., 2014; Jurewicz et al., 2013). The association between DEHP exposure and decreased testosterone did not show a clear response pattern with increasing exposure level or exposure range; however, *medium confidence* studies were more likely to report an association than *low confidence* studies, and *low confidence* studies generally had null, rather than conflicting, results. Given the overall consistency among higher confidence studies, this evidence is considered *moderate*.

Five *medium confidence* studies (Axelsson et al., 2015a; Pan et al., 2015; Meeker and Ferguson, 2014; Specht et al., 2014; Jurewicz et al., 2013) investigated the association between DINP exposure (measured by MINP or MCiOP) and testosterone (Table 14). Three studies (Meeker and Ferguson, 2014; Specht et al., 2014)) found decreasing testosterone levels with increasing DINP exposure; the results in two were statistically significant, including an exposure-response gradient in Specht et al., 2014. The evidence for an association between DINP exposure and decreased testosterone is considered *moderate*.

Evaluation of the association between exposure to DBP (measured by MBP) and testosterone is based on ten studies (Axelsson et al., 2015a; Chang et al., 2015; Den Hond et al., 2015; Pan et al., 2015; Wang et al., 2015c; Han et al., 2014; Meeker and Ferguson, 2014; Jurewicz et al., 2013; Meeker et al., 2009; Pan et al., 2006). Five studies (Pan et al., 2015; Meeker and Ferguson, 2014; Meeker et al., 2009; Pan et al., 2006); Wang et al., 2015b) reported results that indicate decreased testosterone levels with increased DBP exposure (Table 15). The association in one study (Pan et al., 2015) was statistically significant. There was no clear pattern between observed associations and exposure level or range. This evidence is considered *slight*.

Four studies (Chang et al., 2015; Den Hond et al., 2015; Pan et al., 2015; Meeker and Ferguson, 2014) provided data on the association between DIBP exposure (measured by MIBP) and testosterone (Table 15). Of the four studies, three (Chang et al., 2015; Meeker and Ferguson, 2014) (Pan et al., 2015) found decreased testosterone levels with increasing DIBP exposure; the results in two were statistically significant. The fourth study (Den Hond et al., 2015) reported no association, despite having higher exposure levels for MIBP than other studies in this assessment, but was also rated as *low confidence*. Based on the overall consistency, this evidence is considered *moderate*.

Eight studies (Axelsson et al., 2015a; Chang et al., 2015; Den Hond et al., 2015; Wang et al., 2015c; Meeker and Ferguson, 2014; Jurewicz et al., 2013; Meeker et al., 2009) investigated the association between BBP exposure (measured by MBzP) and testosterone (Table 16). Two studies (Pan et al., 2015; Meeker and Ferguson, 2014) reported an inverse association between BBP exposure and testosterone levels, but they were not statistically significant. Results from some of the remaining studies were in the opposite direction (i.e., a positive association). Given the lack of consistency, this evidence is considered to be *indeterminate*.

Nine studies (Axelsson et al., 2015a; Chang et al., 2015; Den Hond et al., 2015; Wang et al., 2015c; Han et al., 2014; Meeker and Ferguson, 2014; Jurewicz et al., 2013; Meeker et al., 2009) (Pan et al., 2015) investigated the association between DEP (measured by MEP) and testosterone (Table 16). Three studies (Pan et al., 2015; Wang et al., 2015c; Meeker and Ferguson, 2014) reported an inverse association between DEP exposure and testosterone levels, but none were statistically significant. Results from some of the remaining studies were in the opposite direction (i.e., a positive association). Given the lack of consistency despite high exposure levels, this evidence is considered *indeterminate*.

In summary, there is *moderate* evidence of an association between exposure to DEHP, DINP, and DIBP and decreased testosterone levels, *slight* evidence for exposure to DBP, and *indeterminate* evidence for BBP and DEP. In the case of BBP, the reporting of no association in the majority of studies may be explained by the lower exposure levels, and corresponding lower sensitivity to observe an effect. Therefore, the results for BBP are not necessarily inconsistent with the results for the other phthalates. DEP, with both a reasonable number of studies and higher exposure levels, showed no clear association with testosterone levels. This lack of association may reflect an inherent difference in potency or activity towards testosterone relative to other phthalates. This difference is consistent with observations from experimental animal studies.

3.6. Other male reproductive effects

In addition to the health effects already described, systematic reviews were performed for hypospadias/cryptorchidism and timing of pubertal development. These reviews are described in detail in the supplemental materials. In summary, for both outcomes, results were largely inconsistent and the evidence was considered *slight* or *indeterminate* for all phthalates.

3.7. Summary of male reproductive effects

Results for all phthalate-outcome combinations are summarized in Fig. 3. Tables 17–21 present the summary of evidence across outcomes within each phthalate with *moderate* or *robust* evidence of male reproductive toxicity.

4. Discussion

With the exception of DEP, all the phthalates included in this systematic review had *moderate* or greater evidence of male reproductive effects; these findings are directly relevant to humans as they generally are based on exposure levels seen in general populations (i.e., not in occupationally exposed settings). The strongest (*robust*) evidence

of male reproductive effects comes from studies of DBP and DEHP in adult males. These two phthalates tended to have the largest number of studies, and exposure levels higher than most of the other phthalates (i.e., DINP, DIBP, and BBP).

The differences in data availability and exposure level/range may explain the differing confidence in the associations between these phthalates and male reproductive effects. For DIBP in particular, which might be expected to have similar activity as DBP due to their similarity in structure, there was a considerably smaller number of available studies and lower exposure levels relative to other phthalates. While it is possible there are differences in potency/activity between these phthalates, at this point, inadequate sensitivity of the systematic review (i.e., low exposure levels, fewer studies) for DINP, BBP, and in particular DIBP seems to be a likely explanation. In light of these issues, it would be inappropriate to conclude that substituting DINP for DEHP or DIBP for DBP would be health protective. In contrast, DEP had a similar number of studies as DBP and generally higher exposure levels, but weaker evidence of an association. This is consistent with experimental animal data that suggest that DEP does not have as strong an anti-androgenic effect as other phthalates (Howdeshell et al., 2008).

The results of this review illustrate the difficulty in drawing conclusions across different phthalates (i.e., do phthalates in general cause male reproductive toxicity?). There is *slight* evidence of an association for most of the individual phthalate/outcome combinations, but these are generally marked by inconsistency across available studies and are difficult to draw conclusions from. Looking at the combinations with *moderate* or *robust* evidence, there is little consistency in which outcomes were strongly associated across the six phthalates. Semen parameters were the most consistent, with four phthalates (DBP, DEHP, BBP, and DINP) having *moderate* or *robust* evidence, and as already discussed, there are reasonable explanations for the differences with DIBP and DEP, but the specific parameters with stronger evidence differed across phthalates (concentration for DBP and DEHP, motility for BBP, and morphology for DINP). While DEHP and DBP both had *robust* evidence overall and *moderate* evidence for anogenital distance, DEHP had stronger evidence for testosterone, while DBP had stronger evidence for time to pregnancy. Still, there are mechanistic linkages between all of these outcomes – low testosterone is associated with decreased anogenital distance and semen quality, semen quality is associated with time to pregnancy – and so there is consistency in a broader sense. Still, more consistency within outcomes, across phthalates, would strengthen the confidence in the overall association between phthalates and male reproductive effects. Additional studies with higher sensitivity (i.e., with repeated exposure measures, higher exposure levels/adequate range, and appropriately powered) would be informative. In addition, more evidence on the cumulative effect of phthalates and confounding across phthalates would help reduce uncertainties.

This systematic review benefited from the involvement of experts on phthalates and male reproductive epidemiology throughout the process, from development of the study evaluation criteria through evidence synthesis. However, one important limitation was that we did not perform quantitative meta-analysis to summarize the findings of the studies. This was generally due to differences in the way results were presented across studies.

Additionally, further review of mechanistic data for specific outcomes may have clarified the relationship, as would review of animal studies. Discussion of some additional issues that apply to all phthalate studies, such as correlations across phthalates, will be presented in a forthcoming editorial.

Despite these limitations, our results support male reproductive effects as a hazard associated with phthalate exposure in humans, which supports recent regulations by the U.S. Consumer Product Safety Commission to ban certain phthalates in children's toys and other products (CPSC 2017, CPSC 2008). Our findings are consistent with other more limited-scope systematic reviews and meta-analyses that examined some of the outcomes discussed here. NAS also found moderate evidence of an association between DEHP and DBP and anogenital distance, while considering the evidence for infant testosterone and hypospadias to be inadequate (National Academies of Sciences, Engineering, and Medicine, 2017). Two meta-analyses on semen parameters and phthalate exposure reported that phthalate exposure was associated with diminished semen quality (Wang et al., 2016a; Cai et al., 2015). This consistency across different review methods provides clear support for our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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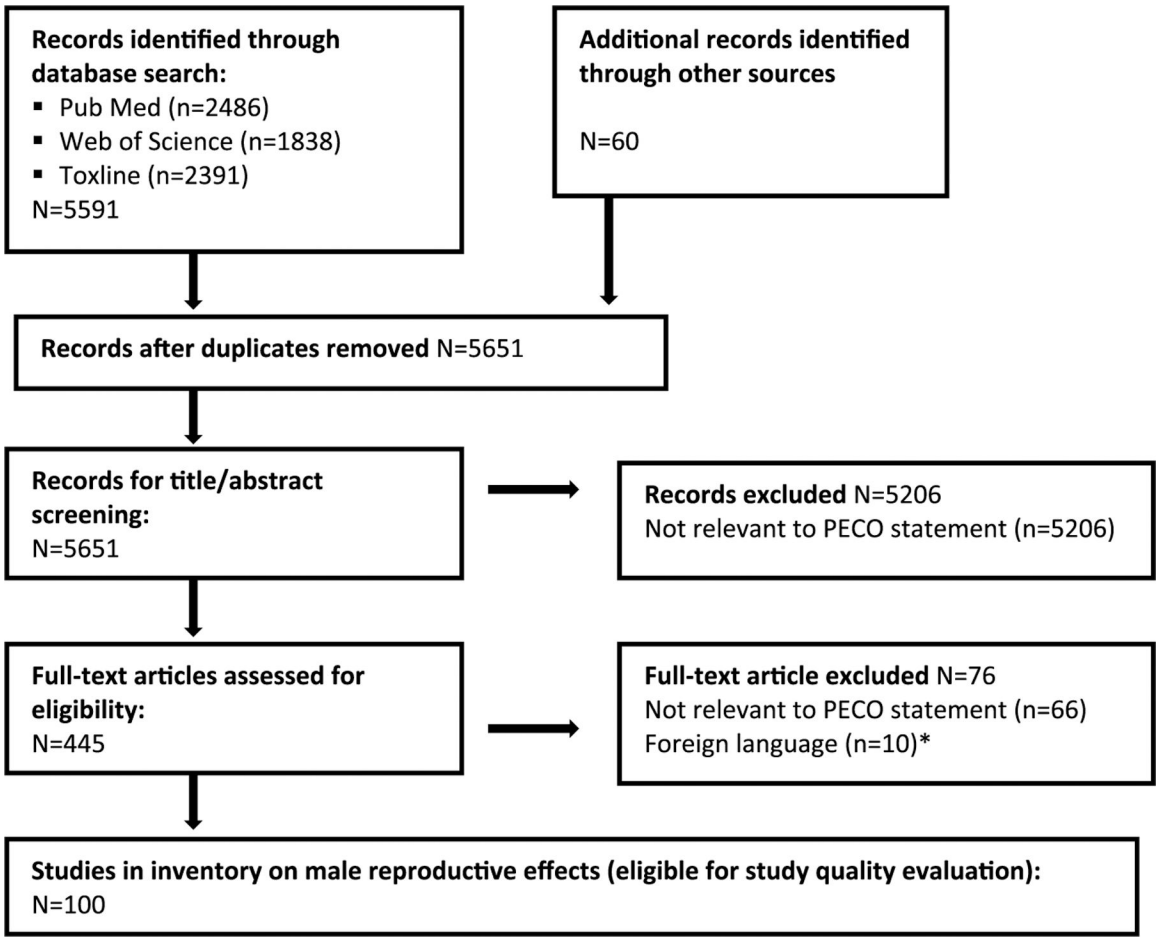
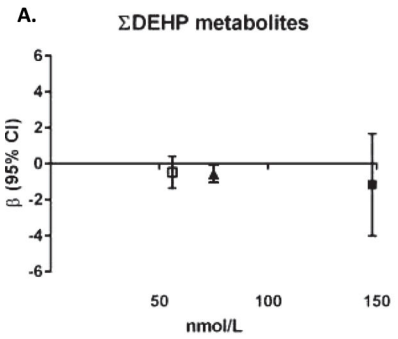


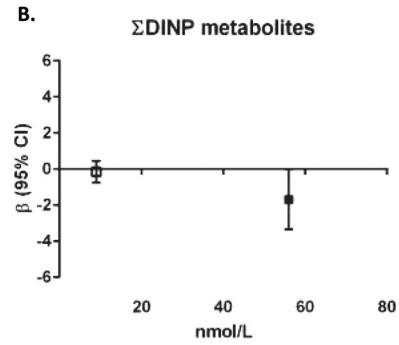
Fig. 1.

Literature flow diagram for male reproductive effects of phthalates.

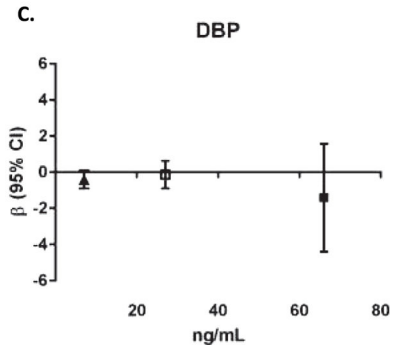
*Did not include studies on male reproductive effects.



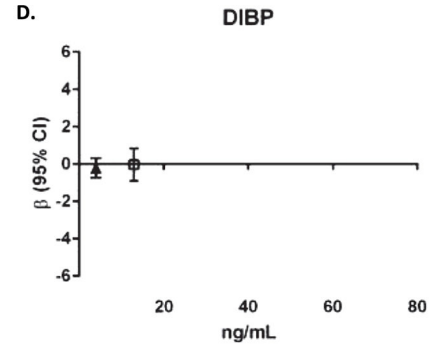
DEHP (measured by sum of DEHP metabolites)		
Reference, study confidence, N	∑DEHP median, 75th percentile (nmol/L)	Continuous AGD_{as} β (95% CI)
□ **Jensen et al., 2016**, Medium, 245	56, 92	−0.47 (−1.35, 0.41)
▲ **Swan et al., 2015**^, Medium, 365	75, 165	−0.55 (−1.04, −0.06)^
■ **Bornehag et al., 2015**, Medium, 196	148, 221	−1.16 (−4.01, 1.68)
DEHP (measured by MEHP, not on graph)		
Swan, 2008^, Low, 106	3, 9	−1.52 (p = 0.017)^
Suzuki et al., 2012, Low, 111	4, 7	−0.23 (−0.41, −0.04)* AGD_{ap}
Bustamante-Montes et al., 2013, Low, 73	4 (mean)	−0.0049 (p = 0.9) (not log transformed)



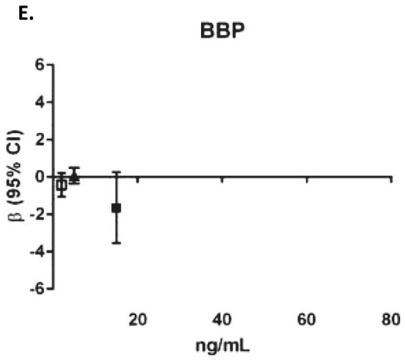
DINP (measured by sum of DINP metabolites)		
Reference, study confidence, N	∑DINP median, 75th percentile (nmol/L)	Continuous AGD_{as} β (95% CI)
□ **Jensen et al., 2016**, Medium, 245	9, 23	−0.15 (−0.75, 0.44)
■ **Bornehag et al., 2015**, Medium, 196	56, 125	−1.69 (−3.35, −0.02)
DINP (measured by MCiOP, not on graph)		
Swan et al., 2015^, Medium, 365	13, 45	0.39 (−0.39, 1.16)^



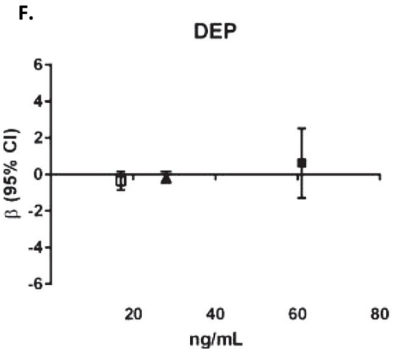
DBP (measured by MBP)		
Reference, study confidence, N	MBP median, 75th percentile (ng/mL)	Continuous AGD_{as} β (95% CI)
▲ **Swan et al., 2015**^, Medium, 365	7, 17	−0.40 (−0.88, 0.09)^
Suzuki et al., 2012, Low, 111	7, 17	Not significant (details not reported)
Swan, 2008^, low, 106	14, 31	−1.41 (p = 0.05)^
□ **Jensen et al., 2016**, Medium, 245	27, 48	−0.13 (−0.89, 0.63)
■ **Bornehag et al., 2015**, Medium, 196	66, 112	−1.41 (−4.39, 1.57)



DIBP (measured by MiBP)		
Reference, study confidence, N	MiBP median, 75th percentile (ng/mL)	Continuous AGDas β (95% CI)
Swan, 2008^, Low, 106	3, 5[a]	−1.28 (p = 0.1)
▲ **Swan et al., 2015**^, Medium, 365	4, 11	−0.21 (−0.73, 0.31)
□ **Jensen et al., 2016**, Medium, 245	13, 23	−0.03 (−0.90, 0.83)



BBP (measured by MBzP)		
Reference, study confidence, N	MBzP median, 75th percentile (ng/mL)	Continuous AGD_{as} β (95% CI)
□ **Jensen et al., 2016**, Medium, 245	3, 6	−0.42 (−1.06, 0.21)
▲ **Swan et al., 2015**^, Medium, 365	3, 9	0.07 (−0.35, 0.49)^
Suzuki et al., 2012, Low, 111	4, 9	Not significant (details not reported)
Swan, 2008^, Low, 106	8, 24	−0.14 (p = 0.8)
■ **Bornehag et al., 2015,** Medium, 196	15, 36	−1.66 (−3.56, 0.25)



DEP (measured by MEP)		
Reference, study confidence, N	MEP median, 75th percentile (ng/mL)	Continuous AGD_{as} β (95% CI)
Suzuki et al., 2012, Low, 111	8, 32	Not significant (details not reported)
□ **Jensen et al., 2016**, Medium, 245	17, 54	−0.34 (−0.84, 0.17)
▲ **Swan et al., 2015**^, Medium, 365	28, 81	−0.14 (−0.45, 0.17)^
■ **Bornehag et al., 2015**, Medium, 196	61, 134	0.63 (−1.29, 2.54)
Swan, 2008^‡, Low 106	128, 437[‡]	−1.27 (p = 0.005)^

Fig. 2.

A–F. Association between phthalate metabolite levels measured in maternal urine samples during pregnancy and AGD in boys.

*$p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ − 0.5), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

^β recalculated to reflect ln transformation of metabolite (from log10).

‡Exposure levels from (Swan et al., 2015).

Exposure level on x-axis is population median for each study, and the axes are scaled the same for all phthalates to facilitate comparison of exposure levels, with the exception of DEHP and DINP, which were reported in nmol/L instead of ng/mL. Each panel depicts results for a metabolite(s) from a different parent phthalate. Studies within each phthalate

are sorted by exposure levels. Effect estimates are change in anogenital distance in mm per ln-unit of exposure.

Timing of exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP
In utero	Anogenital distance	M	S	M	S	S	S
	Hypospadias/cryptorchidism	I	S	S	S	S	I
In utero or childhood	Pubertal development	I	I	I	I	I	I
Adult	Semen parameters	M	M	R	S	M	I
	Time to pregnancy	S	I	M	S	M	I
	Testosterone	M	M	S	M	I	I
	Male repro overall	R	M	R	M	M	S

Robust (R)	Moderate (M)	Slight (S)	Indeterminate (I)
Level of confidence in association			

Fig. 3.
Summary of epidemiologic evidence of male reproductive effects associated with phthalates.

Table 1

Primary outcomes included in the systematic review.

Outcome	Background and relevance to male reproductive toxicity
Anogenital distance (AGD)	• Distance from the anus to the genitalia (sexually dimorphic trait with AGD longer in males than females) (Liu et al., 2014). • Externally visible marker shown in animal studies to be a sensitive indicator of prenatal androgen exposure. Decreases in AGD reflect alterations in androgen levels or function during the masculinization programming window (Dent et al., 2015; Dean and Sharpe, 2013). • Susceptible to anti-androgenic environmental exposures.
Semen parameters	• When a couple experiences difficulty getting pregnant, male factor issues (i.e., semen quality) is the sole factor in about 20% of cases and a contributory cause in another 20–30% (Thonneau et al., 1991).
Time to pregnancy	• Fecundity is the biological capacity to reproduce. Time to pregnancy is the primary outcome measure used to study fecundity. • Time to pregnancy displays a reverse j-shaped cumulative distribution with many couples (30–40% conceiving in the first cycle (Buck Louis et al., 2011) and 80–90% of couples being pregnant after up to 12 months of trying (Gnoth et al., 2003). • Time to pregnancy within a couple can be influenced by either male or female exposures, or both (this review focuses on male exposure). • Increases in time to pregnancy are considered indicative of reproductive toxicity (U.S. EPA (U.S. Environmental Protection Agency), 1996, 30,019).
Testosterone	• Plays an important role in the development of the male reproductive system and is necessary for normal male fertility. • Low testosterone levels are associated with adverse conditions (e.g., abnormal sexual differentiation, decreased fertility (U.S. EPA (U.S. Environmental Protection Agency), 1996).
Hypospadias/ cryptorchidism	• Hypospadias is the abnormal development of the urethra in males, resulting in the location of the opening of the penis on the underside instead of at the tip. • Cryptorchidism, or undescended testes, can be present at birth (congenital cryptorchidism) or can occur later during infancy and childhood (acquired cryptorchidism).
Pubertal development	• Puberty is a continuous process involving maturation of both the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. • Hormonal changes during puberty underlie the natural dynamic period of physical and sexual maturation that culminates in the ability to reproduce. • Either early or delayed pubertal onset is considered an adverse effect (U.S. EPA (U.S. Environmental Protection Agency), 1996).

Table 2

Epidemiology studies of AGD.

	Reference	Study description			Includes metabolites of:						Study evaluation					
		Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis	Overall confidence
Included	(Bornehag et al., 2015)	Birth cohort (N=196 boys) in Sweden	Single urine sample (1st trimester)	AGD at 19–21 mo	✓	✓	✓		✓	✓	A/P	G	G	A	G	Medium
	(Bustamante-Montes et al., 2013)	Birth cohort (N=73 boys) in Mexico	Single urine sample (3rd trimester)	AGD at 1–2 d	✓		✓[a]		✓	✓	P	G	A	A	G	Low
	(Jensen et al., 2016)	Birth cohort (N=273 boys) in Denmark	Single urine sample (26–30 wk gestation)	AGD at 3 mo	✓	✓	✓	✓	✓	✓	A/P	G	G	A	G	Medium
	(Suzuki et al., 2012)	Birth cohort (N=73 boys) in Japan	Single urine sample (3rd trimester)	AGD at 1–3 d	✓		✓		✓	✓	P	A	P	P	A	Low
	(Swan, 2008)	Birth cohort (N=106 boys) in U.S.	Single urine sample (mean 28 wk gestation)	AGD at mean 13 mo (range 1–36)	✓		✓	✓	✓	✓	A/P	P	G	A	P	Low
	(Swan et al., 2015)	Birth cohort (N=365 boys) in U.S.	Single urine sample (1st trimester)	AGD at 1–2 d	✓	✓	✓	✓	✓	✓	A/P	G	A	A	A	Medium
				Total Studies per Phthalate	6	3	5	3	5	5						
	Reference	**Reason for Exclusion**														
Excluded	(Huang et al., 2009)	Critical deficiency in exposure measure (exposure based on amniotic fluid measures)														

G = good; A = adequate; D = deficient; A/D = adequate for short chain phthalates, deficient for long chain phthalates.

[a] Study was considered *critically deficient* for this phthalate due to a high percent below the limit of detection (LOD).

Table 3

Epidemiology studies of semen parameters.

	Reference	Study description			Includes metabolites of:						Study evaluation					
		Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis	Overall confidence
Included	(Axelsson et al., 2015a) (Axelsson et al., 2015b)	Cross-sectional (N=314) in Sweden; men entering military	Single urine sample; subset with prenatal sample available	Concentration, motility, morphology by WHO guidelines	✓	✓	✓		✓	✓	A/P	A	A	A	A	Medium
	(Bloom et al., 2015)	Cohort (N=375) in U.S.; men from couples trying to conceive	Single urine sample	Concentration, motility, morphology by WHO guidelines in two samples	✓		✓	✓	✓	✓	A/P	A	A	A	A	Medium
	(Den Hond et al., 2015)	Case-control (N=40 cases reduced semen quality/80 controls) in Belgium	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓		✓	✓	✓	✓	A/P	G	P	P	A	Low
	(Han et al., 2014)	Cross-sectional (N=232) in China; general population	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓		✓		✓[a]	✓	A/P	G	P	A	A	Medium
	(Hauser et al., 2006)	Cross-sectional (N=463) in U.S.; men from couples seeking infertility workup	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓		✓		✓	✓	A/P	G	A	A	A	Medium
	(Herr et al., 2009)	Cross-sectional (N=349) in Germany; men from	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓						P	A	P	P	P	Low

couples seeking infertility workup															
(Huang et al., 2013) (Huang et al., 2011)	Cross-sectional (N=62) in Taiwan; factory workers and students	Single urine sample, occupational, air sampling	Concentration, motility, morphology by WHO guidelines	✓				A	A	A	P	A	Medium
(Jonsson et al., 2005)	Cross-sectional (N=234) in Sweden; men entering military	Single morning urine sample	Concentration, motility, morphology by WHO guidelines	✓[a]		✓	✓	A	A	A	P	A	Medium
(Jurewicz et al., 2013)	Cross-sectional (N=269) in Poland; men at infertility clinic	Single morning urine sample	Concentration, motility, morphology by WHO guidelines	✓	✓	✓	✓	A/P	A	P	A	A	Medium
(Liu et al.,2012)	Cross-sectional (N=125) in China; men seeking fertility assessment	Two urine samples several days apart	Concentration, motility, morphology by WHO guidelines	✓		✓	✓[a]	G	G	P	P	A	Medium
(Pan et al., 2016); Pan et al., (2015)	Cross-sectional (N=1,066) in China; men seeking fertility assessment	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓	✓	✓	✓	A/P	A	A	A	A	Medium
(Specht et al., 2014) (Lenters et al., 2014)	Cross-sectional (N=589) in Greenland, Poland, Ukraine; men from couples at antenatal visit	Single blood sample (only used for secondary metabolites)	Concentration, motility, morphology by WHO guidelines	✓	✓			P	P	G	A	A	Medium

	Thurston et al. (2016)	Cross-sectional sample (N=420) of male partners from pregnancy cohort in U.S.	Single urine sample	Concentration, motility, morphology by WHO guidelines	✓		✓		✓	✓	A/P	G	A	A	G	Medium
	(Wang et al., 2015b)	Cross-sectional (N=1,040) in China; men seeking semen analysis	Two urine samples collected same day	Concentration, motility, morphology by WHO guidelines	✓		✓		✓	✓	G	G	A	A	G	Medium
	(Wirth et al., 2008)	Cross-sectional (N=45) in U.S.; men seeking fertility assessment	Single morning urine sample	Concentration, motility, morphology by WHO guidelines	✓		✓	✓[a]	✓	✓	A/P	P	P	A	A	Medium
				Total Studies per Phthalate	14	4	12	4	11	12						

	Reference	Reason for Exclusion
Exclu	(Joensen et al., 2012)	Results not presented for individual phthalate metabolites
	(Kranvogl et al., 2014)	Critical deficiencies in multiple evaluation categories
	(Pan et al., 2011)	Critical deficiency in exposure measure (exposure based on measures in semen)
	(Pant et al., 2008)	Critical deficiency in exposure measure (exposure based on measures in semen)
	(Pant et al., 2014)	Critical deficiency in exposure measure (exposure based on measures in semen)
	(Toshima et al., 2012)	Critical deficiency in outcome measure; limited in other categories
	(Wang et al., 2015a)	Critical deficiency in exposure measure (exposure based on measures in semen)

	(Wang et al., 2016b)	Critical deficiency in exposure measure (exposure based on measures in semen); subset of study in Wang et al. (2015b)
	(Zhang et al., 2006)	Critical deficiency in exposure measure (exposure based on measures in semen)

G = good; A = adequate; D = deficient; A/D = adequate for short chain phthalates, deficient for long chain phthalates; WHO=World Health Organization.

[a]Study was considered *critically deficient* for this phthalate due to a high percent below the LOD.

Table 4

Associations between DEHP exposure and semen parameters.

Reference; Study confidence; N	Exposure	Outcome transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
∑DEHP							
Huang et al. (2011); Medium; 45	No transformation, air concentration	No transformation	β (SE; *p*-value)	8/56 (n low/n high exposed) [occupational setting]	−0.19 (0.12; $p = 0.1$)	−0.23 (0.11; $p = 0.04$)	0.014 (0.056, $p = 0.8$) (% abnormal)
(Thurston et al., 2016); Medium; 420	Ln-transformed	Log-transformed	β (CI)	MEOHP mean 13 Range 0.5–1320	0.04 (−0.04,0.11)	0.30 (−0.80,1.41)	0.21 (−0.32,0.74)
Wirth et al. (2008); Medium; 45	Tertiles	Dichotomous	OR (CI)	10.1	T2: 1.97 (0.2, 16.1) T3: 6.65 (0.9, 47.3)	T2: 0.7 (0.1−4.4) T3: 0.7 (0.1−4.4)	T2: 1.2 (0.3, 5.4) T3: 1.1 (0.3, 4.7)
Herr et al. (2009); Low; 349	Quartiles	Dichotomous	OR (CI)	4.4	Q2: 0.86 (0.37, 1.97) Q3: 1.11 (0.46, 2.70) Q4: 1.57 (0.60, 4.08)	Q2: 0.61 (0.2, 1.7) Q3: 0.74 (0.3, 2.2) Q4: 0.86 (0.3, 2.9)	Q2: 1.95 (0.7, 5.2) Q3: 0.91 (0.4, 2.1) Q4: 1.26 (0.57, 2.8)
MEOHP							
Bloom et al. (2015); Medium; 375 [related to Wang et al., 2015a]	Ln-transformed; 1 IQR difference	Box-Cox transformed	β (CI)	5.7	−1.90 (−3.7, −0.2) *	CD	−3.35 (−11.4, 4.7)
Wang et al. (2015b); Medium; 1,040 [related to Bloom et al., 2015]	Ln-transformed	Ln-transformed	β (CI)	5.7	(see row with % change effect estimates)	0.80 (−1.0, 2.6)	−0.10 (−0.8, 0.6)
Huang et al. (2013); Medium; 62	Log transformed	No transformation	β (CI)	18/92 (low/high exposed)	−0.12 (−0.3, 0.06)	−0.02 (−0.3, −0.07)	−0.001 (−0.07, 0.07)
Den Hond et al. (2015); Low; 120	Ln-transformed	No transformation	β (SE) for 1 unit increase	7.7 (mean in controls)	0.18 (0.28)	1.73 (4.15)	−0.12 (0.42)
Specht et al. (2014); Medium; 589	Dichotomous	Ln-transformed	Means (CI)	0.2	<LOD: 51.5 ≥LOD: 46.1 (35.3, 60.1)	Not significant (details not reported)	Not significant (details not reported)
Wang et al. (2015b); Medium; 1,040 [related to Bloom et al., 2015]	Ln-transformed	Ln-transformed	% change (CI)	5.7	4.08% (−9.4, 17.4)	(see results for β effect estimates)	(see row with β effect estimates)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	Cubic root for concentration	% change (CI)	8.4 IQR 4.8–14.3	−1.3% (−3.6,1.0)	−0.5% (−3.6,2.5)	−2.1% (−5.4,1.2)
Axelsson et al. (2015a); Medium; 314	Quartiles	Cubic root	Mean difference (Q4 vs. Q1)	9.6	−0.06 (−0.48, 0.36)	−6.9 (−13, −1.1) *	−0.42 (−2.4, 1.6)

Reference; Study confidence; N	Exposure	Outcome transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
Wang et al. (2015b); Medium; 1040	Quartiles	Dichotomous	OR (CI)	5.7 7.0	Q2: 0.97 (0.53, 1.79) Q3: 0.82 (0.43, 1.55) Q4: 0.86 (0.47, 1.60)	Q2: 0.86 (0.6, 1.2) Q3: 0.90 (0.6, 1.3) Q4: 0.73 (0.5, 1.1)	
Liu et al. (2012); Medium; 125	Tertiles	Dichotomous	OR (CI)	2.7 (mean)	T2: 1.4 (0.3, 7.7) T3: 0.6 (0.1, 4.2)	T2: 1.0 (0.4, 3.1) T3: 0.6 (0.2, 1.8)	
Hauser et al. (2006); Medium; 463	Quartiles	Dichotomous	OR (CI)	32.1	Q2: 3.1 (0.8, 11.7) Q3: 1.1 (0.3, 4.6) Q4: 1.6 (0.4, 6.3)	Q2: 0.9 (0.4, 2.0) Q3: 0.6 (0.3, 1.3) Q4: 0.8 (0.3, 1.6)	Q2: 1.4 (0.5, 3.7) Q3: 0.5 (0.2, 1.5) Q4: 0.7 (0.3, 2.0)
MEHP							
Jurewicz et al. (2013); Medium; 269	Log transformed	Log transformed	β (p)	8.8	−0.07 (p = 0.3)	−3.85 (p = 0.001) *	1.29 (p = 0.24)
Huang et al. (2013); Medium; 62 (see also means ± SD results)	Log transformed	No transformation	β (CI)	6.3/23[a]	−0.07 (−0.6, 0.5)	−0.55 (−1.0, −0.1)	0.09 (−0.1, 0.3)
Huang et al. (2013); Medium; 62 (see also β results)	Categorical		Means ± SD	6.3/23[a]	Controls: 46.7 ± 32.0 Low: 19.9 ± 14.6 High: 27.8 ± 25.5	Controls: 65.2 ± 10.0 Low: 56.1 ± 18.3 High: 41.4 ± 22.0	Controls: 44.8 ± 7.7 Low: 41.4 ± 9.3 High: 41.4 ± 11.6
Han et al. (2014); Medium; 232	Dichotomous	Dichotomous	OR (CI)	1.1 5th–95th percentile: 0−24	1.15 (0.57, 2.33)	0.48 (0.08, 2.76)	1.18 (0.58, 2.39)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile; T = tertile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 5

Associations between DINP exposure and semen parameters.

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
MCiOP							
Specht et al. (2014); Medium; 589	Tertiles	Ln-transformed	Means (CI) by percentile e group	0.5 maximum: 42	<25th: 52.8 (43.9, 63.7) 25th–75th: 52.2 (45.1, 60.3) >75th: 51.8 (43.1, 62.2)		
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	Cubic root for concentration	% change (CI)	1.2 IQR: 0.7–2.1	−1.2% (−3.4, 0.9)	−2.4% (−5.2, 0.4%)	−3.4% (−6.4, 0.3)
Axelsson et al. (2015a); Medium; 314	Quartiles	Cubic root	Mean difference (Q4 vs. Q1)	16 range: 1.4−810	−0.08 (−0.49, 0.33)	−1.3 (−7.2, 4.6)	−1.2 (−3.1, 0.81)
MINP							
Jurewicz et al. (2013); Medium; 269	Log transformed	Log transformed	β (p)	1.1 IQR: 0.2−6.4	−0.31 (0.191)	6.21 (0.060)	−9.05 (0.033)*
Specht et al. (2014); Medium; 589	Tertiles	Ln-transformed	Means (CI) by percentile group	0.003 Proxy-MINP (nm) 0.15 (maximum)	<25th: 50.3 (37.8, 67.1) 25th–75th: 48.7 (37.4, 63.4) >75th: 45.5 (34.2, 60.4)		

*$p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile; T = tertile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 6

Associations between DBP and semen parameters.

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	MBP (ng/mL) [median unless otherwise specified]	Sperm concentration (×10^6/ml)	Motility (% normal)	Morphology (% normal)
Wang et al. (2015b); Medium; 1,040	Continuous ln-transformed	No transformation	β (CI)	70	(see row with change effect estimates)	−0.92 (−2.58, 0.75)	−0.40 (−1.07, 0.27)
Bloom et al. (2015); Medium; 375	Continuous ln-transformed; 1 IQR difference	Box-Cox transformed	β (CI)	7	−0.95 (−4.0, 2.1)	−1.22 (−4.0, 1.6)	−7.03 (−21.0, 6.9)
Thurston et al. (2016); Medium; 420	Ln-transformed	Log-transformed	β (CI)	15	0.01 (−0.09,0.11)	−0.58 (−2.00, 0.84)	0.22 (−0.46, 0.91)
Jurewicz et al. (2013); Medium; 269	Continuous log transformed	Log transformed (concentration)	β (p)	83	−0.21 (p = 0.11)	−1.55 (p = 0.5)	−2.68 (p = 0.2)
Den Hond et al. (2015); Low; 120	Continuous ln-transformed	No transformation	β (SE)	18.9; 20.7 (mean controls; cases)	0.24 (0.35)	4.21 (5.20)	−0.25 (0.42)
Wang et al. (2015b); Medium; 1,040	Continuous ln-transformed	Ln-transformed (concentration)	% change (CI)	70	−6.18% (1.6, −0.3)	(see row with β effect estimates)	(see row with β effect estimates)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	Cubic root for concentration	% change (CI)	78	−2.4% (−5.1,0.3)	−1.3% (−4.8,2.3)	−6.5 (−10.3,− 2.7) *
Axelsson et al. (2015a); Medium; 314	Quartiles	Cubic root (concentration)	Mean difference (Q4 vs. Q1)	47	0.04 (−0.38, 0.45)	−7.7 (−14, −1.8) *	0.65 (−1.3, 2.6)
Jonsson et al. (2005); Medium; 234	Quartiles	No transformation	Mean difference (Q4 vs. Q1)	78	−7.9 (−33, 17)	2.1 (−4.0, 8.2)	
Wang et al. (2015b); Medium; 1,040	Quartiles	Dichotomous	OR (CI)	70	Q2: 1.28 (0.7, 2.5) Q3: 0.87 (0.4, 1.8) Q4: 2.01 (1.1, 3.8) *	Q2: 0.74 (0.5, 1.1) Q3: 0.96 (0.7, 1.4) Q4: 1.04 (0.7, 1.5)	
Hauser et al. (2006); Medium; 463	Quartiles	Dichotomous	OR (CI)	18	Q2: 3.1 (1.2, 8.1) * Q3: 2.5 (0.9, 6.7) Q4: 3.3 (1.2, 8.5) *	Q2: 1.5 (0.8, 2.6) Q3: 1.5 (0.8, 2.6) Q4: 1.8 (1.1, 3.2) *	Q2: 0.8 (0.4, 1.6) Q3: 0.9 (0.5, 1.7) Q4: 0.8 (0.4, 1.6)
Han et al. (2014); Medium; 232	Dichotomous	Dichotomous	OR (CI)	19	1.97 (0.97, 4.0)	1.08 (0.7, 1.7)	1.53 (0.8, 3.1)
Reference; Study Confidence Rating; N	**Exposure**	**Outcome transformation**	**Effect estimate**	**MBP (ng/mL) [median unless otherwise specified]**	**Sperm concentration (×10^6/ml)**	**Motility (% normal)**	**Morphology (% normal)**
Wirth et al. (2008); Medium; 45	Dichotomous	Dichotomous	OR (CI)	25	0.5 (0.1, 3.6)	0.8 (0.2, 3.9)	3.3 (0.7, 16.2)

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	MBP (ng/mL) [median unless otherwise specified]	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
Liu et al. (2012); Medium; 125	Tertiles	Dichotomous	OR (CI)	26 (mean)	Q2: 6.8 (0.6, 75.3) Q3: 12.0 (1.0, 143) *	Q2: 0.5 (0.2, 1.4) Q3: 0.7 (0.3, 2.1)	Q2: 1.0 (0.3, 4.1) Q3: 0.4 (0.1, 2.1)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile; T = tertile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 7

Associations between DIBP and semen parameters.

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	MIBP median (ng/mL)	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
Thurston et al. (2016); Medium; 420	Ln-transformed	Log-transformed	β (CI)	2.8	0.02 (−0.06,0.11)	0.82 (−0.31,1.96)	0.28 (−0.27,0.83)
Bloom et al. (2015); Medium; 375	Continuous ln transformed; 1 IQR difference	Box-Cox transformed	β (CI)	4.4	0.46 (−1.90,2.83)	−0.98 (−3.16,1.20)	−4.43 (−15.15,6.29)
Den Hond et al. (2015); Low; 120	Continuous ln-transformed	Continuous, no transformation noted	β (SE)	55 (mean)	0.16 (0.53)	4.81 (3.59)	0.10 (0.33)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	Cubic root for conc	% change (CI)	48	−2.1% (−4.6,0.4)	−2.2% (−5.4,1.1)	−5.3% (−8.9,−1.8) *

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile; T = tertile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 8

Associations between BBP and semen parameters.

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	MBzP median (ng/mL)	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
Wang et al. (2015b); Medium; 1,040	Ln-transformed	No transformation	β (CI)	2.9	(see row with % change effect estimates)	0.43 (−0.62, 1.47)	0.20 (−0.22, 0.61)
Bloom et al. (2015); Medium; 375	Ln-transformed; 1 IQR difference	Box-Cox transformed	β (CI)	3.6	−3.09 (−5.52, −0.66) *	−1.67 (−3.92, 0.58)	−5.71 (−16.97, 5.56)
Thurston et al. (2016); Medium; 420	Ln-transformed	Log-transformed	β (CI)	11	−0.04 (−0.12,0.04)	−1.47 (−2.61,−0.33) *	−0.19 (−0.75,0.36)
Jurewicz et al. (2013); Medium; 269	Log transformed	Log transformed (concentration)	β (p)	5.2	−0.07 (p = 0.25)	1.86 (0.10)	1.17 (0.28)
Den Hond et al. (2015); Low; 120	Ln-transformed	No transformation	β (SE)	4.5 (mean controls)	−0.03 (0.17)	−1.44 (2.57)	0.30 (0.27)
Wang et al. (2015b); Medium; 1,040	Ln-transformed	Ln-transformed (concentration)	% change (CI)	2.9	1.01% (−3.05, 5.13%)	(see row with β effect estimates)	(see row with β effect estimates)
(Pan et al., 2016); Pan et al. (2015);	Ln-transformed Medium; 1,066	Cubic root for conc	% change (CI)	0.1	−3.4% (−5.9,−0.8) *	−1.8% (−5.1,1.6)	−4.0% (−7.6,−0.4) *
Axelsson et al. (2015a); Medium; 314	Quartiles	Cubic root (concentration)	Mean difference (Q4 vs. Q1)	13	−0.29 (−0.71, 0.13)	−5.4 (−11, 0.56)	−0.79 (−2.8, 1.2)
Reference; Study Confidence Rating; N	**Exposure**	**Outcome transformation**	**Effect estimate**	**MBzP median (ng/mL)**	**Sperm concentration ($\times 10^6$/ml)**	**Motility (% normal)**	**Morphology (% normal)**
Jonsson et al. (2005); Medium; 234	Quartiles	No transformation	Mean difference (Q4 vs. Q1)	16	7.2 (−16, 31)	−4.3 (−10, 1.6)	
Wang et al. (2015b); Medium; 1,040	Quartiles	Dichotomous	OR (CI)	2.9	Q2: 0.88 (0.48, 1.61) Q3: 0.83 (0.44, 1.53) Q4: 0.85 (0.46, 1.58)	Q2: 0.75 (0.51, 1.09) Q3: 1.05 (0.73, 1.52) Q4: 0.93 (0.64, 1.35)	
Hauser et al. (2006); Medium; 463	Quartiles	Dichotomous	OR (CI)	8.0	Q2: 1.1 (0.4, 2.6) Q3: 1.1 (0.4, 2.5) Q4: 1.9 (0.8, 4.3)	Q2: 1.3 (0.7, 2.3) Q3: 1.3 (0.8, 2.3) Q4: 1.3 (0.7, 2.3)	Q2: 0.7 (0.3, 1.4) Q3: 0.9 (0.4, 1.7) Q4: 1.1 (0.6, 1.6)
Wirth et al. (2008); Medium; 45	Dichotomous	No transformation	OR (CI)	17	1.4 (0.3, 6.3)	1.3 (0.3, 5.5)	0.9 (0.2, 3.2)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 9

Associations between DEP and sperm parameters.

Reference; Study Confidence Rating; N	Exposure	Outcome transformation	Effect estimate	MEP median (ng/mL)	Sperm concentration ($\times 10^6$/ml)	Motility (% normal)	Morphology (% normal)
Wang et al. (2015b); Medium; 1,040	Ln-transformed	No transformation	β (CI)	18	(see row with % change effect estimates)	0.12 (−0.77, 1.02)	−0.25 (−0.60, 0.11)
Bloom et al. (2015); Medium; 375	Ln-transformed; 1 IQR difference	Box-Cox transformed	β (CI)	86	−1.01 (−2.86, 0.85)	−0.83 (−2.54, 0.88)	−1.23 (−9.64, 7.17)
Thurston et al. (2016); Medium; 420	Ln-transformed	Log-transformed	β (CI)	201	−0.02 (−0.07,0.04)	−0.13 (−0.95,0.69)	0.16 (−0.24,0.55)
Jurewicz et al. (2013); Medium; 269	Log-transformed	Log transformed	β (p) (concentration)	45	−0.07 (0.25)	−3.85 (0.001)*	1.29 (0.24)
Reference; Study Confidence Rating; N	**Exposure**	**Outcome**	**Effect transformation estimate**	**MEP median (ng/mL)**	**Sperm concentration ($\times 10^6$/ml)**	**Motility (% normal)**	**Morphology (% normal)**
Den Hond et al. (2015); Low; 120	Ln-transformed	No transformation noted	β (SE)	50 (mean controls)	0.24 (0.19)	4.62 (2.78)	0.05 (0.24)
Wang et al. (2015b); Medium; 1,040	Ln-transformed	Ln-transformed (concentration)	% change (CI)	18	1.01% (−2.02, 4.08%)	(see row with β effect estimates)	(see row with β effect estimates)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	Cubic root (concentration)	% change (CI)	13	−1.1% (−3.5,1.3)	0.6% (−2.5,3.8)	−1.7% (−5.1,1.8)
Axelsson et al. (2015a); Medium; 314	Quartiles	Cubic root (concentration)	Mean difference (Q4 vs. Q1)	41	0.17 (−0.24, 0.59)	2.6 (−3.3, 8.5)	−0.73 (−2.7, 1.3)
Jonsson et al. (2005); Medium; 234	Quartiles	No transformation	Mean difference (Q4 vs. Q1)	240	5.0 (−15, 25)	−0.4 (−6.4, 5.6)	
Wang et al. (2015b); High; 1,040	Quartiles	Dichotomous	OR (CI)	18	Q2: 1.05 (0.56, 1.98) Q3: 0.94 (0.50, 1.79) Q4: 1.08 (0.58, 2.04)	Q2: 0.88 (0.60, 1.29) Q3: 1.02 (0.71, 1.49) Q4: 0.93 (0.63, 1.36)	
Hauser et al. (2006); Medium; 463	Quartiles	Dichotomous	OR (CI)	158	Q2: 1.5 (0.7, 3.6) Q3: 1.0 (0.4, 2.5) Q4: 1.2 (0.5, 3.0)	Q2: 1.1 (0.6, 1.9) Q3: 0.8 (0.5, 1.5) Q4: 1.0 (0.6, 1.8)	Q2: 0.8 (0.4, 1.6) Q3: 0.7 (0.3, 1.3) Q4: 0.5 (0.3, 1.1)
Han et al. (2014); Medium; 232	Dichotomous	Dichotomous	OR (CI)	3.1	0.78 (0.38, 1.58)	0.96 (0.18, 5.04)	0.88 (0.44, 1.75)
Wirth et al. (2008); Medium; 45	Tertiles	Dichotomous	OR (CI) 108		Q2: 3.6 (0.4, 34.6) Q3: 6.5 (0.6, 73.4)	Q2: 0.7 (0.1, 3.7) Q3: 0.5 (0.1, 2.9)	Q2: 4.2 (0.7, 24.5) Q3: 7.0 (1.0, 48.0)*
Liu et al. (2012); Medium; 125	Tertiles	Dichotomous	OR (CI)	175 (mean)	Q2: 1.4 (0.2, 8.8) Q3: 1.5 (0.2, 9.6)	Q2: 0.7 (0.2, 1.9) Q3: 0.4 (0.1, 1.2)	Q2: 0.2 (0.1, 1.2) Q3: 0.8 (0.2, 3.0)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile. Studies are sorted by study confidence level within each metabolite-effect estimate grouping.

Table 10

Epidemiology studies of time to pregnancy (male exposure).

	Reference	Study description			Includes metabolites of:						Study evaluation					
		Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis	Overall confidence
Included	Buck Louis et al. (2014)	Cohort (N=501) in U.S. of couples trying to conceive	Single urine sample at study entry	Cycles to conception (from pregnancy testing, journals, and fertility monitor)	✓	✓[a]	✓	✓	✓	✓	A/P	G	G	A	A	High
Excluded	**Reference**	**Reason for Exclusion**														
	Modigh et al. (2002)	Critical deficiency in exposure measure (exposure measured after outcome from occupational records, not validated														
	Specht et al. (2015)	Critical deficiency in exposure measure (exposure measured after outcome, during pregnancy)														

G = good; A = adequate; D = deficient; A/D = adequate for short chain phthalates, deficient for long chain phthalates.

[a] Study was considered *critically deficient* for this phthalate due to a high percent below the LOD.

Table 11

Association between phthalate metabolites and time to pregnancy in Buck Louis et al. (2014).

Phthalate (metabolite)	Exposure Geometric mean (ng/mL)	Fecundability Ratio (95% CI)
DINP (MINP)	0.07	1.01 (0.90, 1.14)
BBP (MBzP)	2.8	0.77 (0.65, 0.92)*
DIBP (MiBP)	3.4	0.88 (0.74, 1.04)
DBP (MBP)	5.9	0.82 (0.70, 0.97)*
DEHP (MEOHP)	6.1	0.91 (0.79, 1.05)
DEP (MEP)	82.7	1.01 (0.86, 1.18)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≤ 0.7), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Table 12

Epidemiology studies of testosterone.

	Reference	Study description			Includes metabolites of:						Study evaluation					
		Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis	Overall confidence
Included	Axelsson et al., 2015(a); Axelsson et al., 2015(b)	Cross-sectional (N=314) in Sweden; men entering military	Single urine sample; subset with prenatal sample available	Total T by immunoassay, morning blood sample	✓	✓	✓		✓	✓	A/P	G	A	A	A	Medium
	Chang et al. (2015)	Case-control based on achieving pregnancy (N=141 cases, 35 controls) in Taiwan	Single urine sample	T by immunoassay; morning blood sample	✓		✓	✓	✓	✓	A/P	G	P	P	P	Low
	Den Hond et al., 2015	Case-control (N=40 cases reduced semen quality/80 controls) in Belgium	Single urine sample	T by immunoassay, adjusted for blood collection time in model	✓		✓	✓	✓	✓	A/P	G	P	P	A	Low
	Han et al., 2014	Cross-sectional (N=232) in China; general population	Single urine sample	T by immunoassay, morning blood sample	✓		✓		✓[a]	✓	A/P	G	P	A	A	Medium
	Jurewicz et al., 2013	Cross-sectional (N=269) in Poland; men at infertility clinic	Single morning urine sample	T by immunoassay, morning blood sample	✓	✓	✓		✓	✓	A/P	A	P	A	A	Medium
	Meeker and Ferguson (2014)	Cross-sectional (N=427) in U.S.;	Single urine sample	Total T by mass spectrometry, adjusted for	✓	✓	✓	✓	✓	✓	A/P	A	G	A	A	Medium

	general population	blood collection time in model												
Meeker et al. (2009)	Cross-sectional (N=425) in U.S.; men from subfertile couples	Single urine sample	Total T by immunoassay, adjusted for blood collection time	✓		✓		✓	A/P	A	G	A	G	Medium
Mendiola et al. (2011)	Male partners from pregnancy cohort (N=363)	Single urine sample	Total T by immunoassay, adjusted for blood collection time in model	✓					P	A	G	A	A	Medium
Pan et al. (2006)	Cross-sectional (N=137) in China; PVC (exposed) and construction (unexposed) workers	Single urine sample	Free T by immunoassay, morning blood sample	✓	✓				A/P	G	P	P	P	Low
(Pan et al., 2016); Pan et al. (2015)	Cross-sectional (N=1,066) in China; men seeking fertility assessment	Single urine sample	Total T by immunoassay, adjusted for blood collection time in model	✓	✓	✓	✓	✓	A/P	A	A	A	A	Medium
Park et al. (2010)	Cross-sectional (N=25) in Korea, men working in dental labs	Single pre-shift urine sample	T by immunoassay, morning blood sample	✓					P	P	P	P	P	Low
Specht et al., 2014; Lenters et al., 2014;	Cross-sectional (N=589) in Greenland, Poland, Ukraine; men from couples at antenatal visit	Single blood sample	T by immunoassay, morning blood sample	✓	✓				P	A	G	A	A	Medium

	Wang et al. (2015c)	Cross-sectional (N=1,040) in China; men seeking semen analysis	Two urine samples collected same day	Total T by direct chemilumin-escence assay, morning blood sample	✓		✓		✓	✓	G	G	A	A	G	Medium
				Total Studies per Phthalate	13	5	10	4	8	9						

	Reference	Reason for Exclusion
Excluded	Fong et al. (2015)	No discussion of or adjustment for collection time of outcome sample.
	Janjua et al. (2007)	Critical deficiency in exposure measure (exposure based on measurement in blood)
	Joensen et al. (2012)	Results not presented for individual phthalate metabolites
	Jonsson et al. (2005)	No discussion of or adjustment for collection time of outcome sample.
	Li et al. (2011)	Critical deficiency in exposure measure (exposure based on measurement in blood, semen; diesters analyzed)
	Pant et al. (2014)	Critical deficiency in exposure measure (exposure based on measurement in semen
	Xu et al. (2015)	Results not presented for individual phthalate metabolites
	Wang et al. (2016b)	Critical deficiency in exposure measure (exposure based on measurement in semen) (note: same study as Wang et al. (2015b))

T = testosterone; G = good; A = adequate; D = deficient; A/E = adequate for short chain phthalates, deficient for long chain phthalates.

[a]Study was considered *critically deficient* for this phthalate due to a high percent below the LOD.

Table 13

Associations between DEHP exposure and testosterone.

Reference; Study confidence; N	Transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Exposure IQR (or as specified)	Testosterone effect estimate
∑DEHP					
Mendiola et al. (2011); Medium; 363	Log10 transformed	β (95% CI) for 1 unit increase	0.24 nmol/mL	0.1–0.5	−0.01 (−0.04, 0.03)
Meeker et al. (2009); Medium; 425	Ln-transformed exposure	β (95% CI) for IQR increase	0.31 nmol/mL	0.2–0.7	−6.35 (−17.8, 5.1)
Chang et al. (2015); Low; 176	Ln-transformed exposure and outcome	β (95% CI) for IQR increase	0.15 nmol/mL (mean)		0.98 (0.9, 1.1)Ŧ
Wang et al. (2015c); Medium; 1,040	Ln-transformed exposure and outcome	% difference (95% CI) 1 unit increase	7.9 (MEOHP)	3.9–8.5	−3.7% (−8.0, 0.6)
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	4.9 (MEOHP)	3.0–7.4	−8.42% (−24.5, 11.0)
267 (20–40 yr)			4.2 (MEOHP)	2.8–7.1	0.42 (−5.8, 7.1)
Specht et al. (2014); Medium; 589		Means (95% CI) for <25th, 25th–75th, >75th percentile	0.01 nM (Proxy DEHP)	0.01–0.14	Q1: 15.4 (14.3–16.7) Q2: 14.8 (14.0, 15.7) Q3: 14.1 (13.1–15.1) *p* trend <0.05
MEOHP					
Den Hond et al. (2015); Low; 120	Ln-transformed exposure	β ± SE	7.7	3.9–14.0	−0.03 ± 0.04
Pan et al., 2016; Pan et al. (2015); Medium; 1,066	Ln-transformed exposure and outcome	% change (CI)	8.4	4.8–14.3	−1.6% (−2.2,1.0)
Axelsson et al. (2015a); Medium; 314	Ln-transformed exposure and outcome	Mean difference (Q4 vs. Q1)	9.6	0.5–1,100 (range)	−1.0 (−9.7, 8.7)
Park et al. (2010); Low; 25	Ln-transformed exposure	Correlation coefficient	14 (pre-shift)	9.2–19	−0.33 (*p* = 0.1)
MEHP					
Jurewicz et al. (2013); Medium; 269	Log-transformed exposure	β (p)	8.8	0.6–136 (range)	−0.29 (*p* = 0.04)
Han et al. (2014); Medium; 232	None reported	Partial correlation coefficient	1.1	0.0–23.8 (5th–95th)	−0.05
Pan et al. (2006); Medium; 137	Log10 transformed outcome	Partial correlation coefficient	562/5 μg/g creatinine (exposed/unexposed)	210–1,884/3.7–10	−0.2 (free testosterone)

*$p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile.

Ŧ Coefficient was calculated by study authors with back-transformation of both hormone and phthalate metabolite concentrations. A coefficient < 1.0 indicates a multiplicative decrease in hormone level for an IQR change in exposure.

Units for testosterone differed across studies: ng/mL (Jurewicz et al., 2013, Meeker and Ferguson, 2014, nmol/L (Han et al., 2014, Axelsson et al., 2015a, 2015b, Mendiola et al., 2011, Chang et al., 2015, Pan et al., 2015), nmol/mL (Specht et al., 2014), pg/mL (Pan et al., 2006), ng/dL (Meeker et al., 2009; Den Hond et al., 2015; Wang et al., 2015a, 2015b, 2015c).

Table 14

Associations between DINP exposure and testosterone.

Reference; Study confidence; N	Transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Exposure IQR (or as specified)	Testosterone effect estimate
MINP					
Jurewicz et al. (2013); Medium; 269	Log-transformed exposure	β (p)	1.1	0.2–6.4	0.30 (0.373)
Specht et al. (2014); Medium; 589	Ln-transformed	Means (CI) for <25th, 25th–75th, >75th percentile	0.003 Proxy-MINP (nm)	0.15 (maximum)	Q1: 15.3 (14.2, 16.4) Q2: 14.9 (14.0, 15.8) Q3: 13.9 (12.9, 14.9) *p* trend <0.05
MCiOP					
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed	% change (CI)	1.2	0.7–2.1	−2.3% (−4.5,−0.1) *
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	14	7.76−43.1	−22.5% (−36.7, −5.18)
267 (20–40 yr)			23	9.28–57.0	−0.33 (−7.09, 6.92)
Axelsson et al. (2015a); Medium; 314	Ln-transformed exposure and outcome	Mean difference (95% CI) Q4 vs. Q1	16	1.4–810 (range)	4.3 (−4.9, 14)

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Q = quartile.

Units for testosterone differed across studies: ng/mL (Jurewicz et al., 2013; Meeker and Ferguson, 2014), nmol/L (Pan et al., 2015), nmol/mL (Specht et al., 2014).

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Table 15

Associations between DBP and DIBP exposure and testosterone.

Reference; Study confidence; N	Transformation estimate	Effect	Metabolite (ng/mL) [median unless otherwise specified]	Exposure IQR (or as specified)	Testosterone effect estimate
DBP (measured by MBP)					
Meeker et al. (2009); Medium; 425	Ln-transformed exposure and outcome (except testosterone)	β (95% CI) for IQR increase	17.7	10.6−32.75	−4.65 (−15.7, 6.33)
Jurewicz et al. (2013); Medium; 269	Log-transformed exposure	β (p)	83	19−1,530 (range)	0.02 (p = 1.0)
Den Hond et al. (2015); Low; 120	Ln-transformed exposure	β ± SE	19	12−42	−0.03 (0.03)
Chang et al. (2015); Low; 176	Ln-transformed exposure and outcome	β (95% CI) for IQR increase ∓	11.1 (fertile mean)		0.96 (0.90, 1.02)
Wang et al. (2015c); High; 1,040	Ln-transformed exposure and outcome	% difference (95% CI) 1 unit increase	70	28−84	−1.1% (−4.6, 2.3)
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	8.9	5.0−14.3	−19.3% (−37.0, 3.34)
267 (20–40 yr)			7.0	3.9−11.2	−3.85% (−11.0, 3.89)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed exposure and outcome	% change (CI)	78	39–162	−3.9% (−6.6,−1.1) *
Axelsson et al. (2015a); Medium; 314	Ln-transformed exposure and outcome	Mean difference for Q4 vs. Q1 (95% CI)	47	1.0, 690 (range)	2.1 (−11, 7.6)
Han et al. (2014); Medium; 232	None reported	Partial correlation coefficient	18.72	2.10−129.34 (5^{th}–95^{th})	0.10
Pan et al. (2006); Medium; 137	Log10 transformed outcome	Partial correlation coefficient	548/113 μg/g (exposed/ unexposed)	252–1,493/75–207	−0.253 (free testosterone)
DIBP (measured by MIBP)					
Den Hond et al. (2015); Low; 80/163	Ln-transformed exposure	β ± SE	55	27.0–113.0	0.00 ± 0.03
Chang et al. (2015); Low; 176	Ln-transformed exposure and outcome	β (95% CI) for IQR increase∓	7.6 (fertile mean)		0.92 (0.87, 0.98) *
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	7.3	4.3–11.4	−19.9 (−39.4, 5.83)
267 (20–40 yr)			5.1	3.5−9.1	0.39 (−6.26, 7.52)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed exposure and outcome	% change (CI)	48	28–84	−4.1% (−6.7,−1.5) *

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Ŧ Coefficient was calculated by study authors with back-transformation of both hormone and phthalate metabolite concentrations. A coefficient < 1.0 indicates a multiplicative decrease in hormone level for an IQR change in exposure.

Units for testosterone differed across studies: ng/mL (Jurewicz et al., 2013, Meeker and Ferguson, 2014), nmol/L (Han et al., 2014; Axelsson et al., 2015a, 2015b; Chang et al., 2015; Pan et al., 2015), nmol/mL (Specht et al., 2014), pg/mL (Pan et al., 2006), ng/dL (Meeker et al., 2009, Den Hond et al., 2015, Wang et al., 2015a, 2015b, 2015c).

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Table 16

Associations between BBP and DEP exposure and testosterone.

Reference; Study confidence; N	Transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Exposure IQR (or as specified)	Testosterone effect estimate
BBP (measured by MBzP)					
Meeker et al. (2009); Medium; 425	Ln-transformed exposure and outcome (except testosterone)	β (95% CI) for IQR increase	8.2	4.20−15.9	4.58 (−7.91, 17.0)
Jurewicz et al. (2013); Medium; 269	Log-transformed exposure	β (p)	5.2	0.4−205 (range)	−0.09 (p = 0.5)
Den Hond et al. (2015); Low; 120	Ln-transformed exposure	β ± SE	4.5	2.5−9.0	−0.02 ± 0.02
Chang et al. (2015); Low; 176	Ln-transformed exposure and outcome	β (95% CI) for IQR increase₸	0.7 (fertile mean)		0.96 (0.91, 1.02)
Wang et al. (2015c); Medium; 1,040	Ln-transformed exposure and outcome	% difference (95% CI) 1 unit increase	2.9	1.0−3.4	−1.2% (−5.3, 2.9)
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	5.8	3.6−11.3	−21.1 (−38.6, 1.30)
267 (20–40 yr)			3.7	2.2−6.7	−4.92 (−12.9, 3.82)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed exposure and outcome	% change (CI)	0.1	<LOD-0.4	−2.6% (−5.3,0.1)
Axelsson et al. (2015a); Medium; 314	Ln-transformed exposure and outcome	Mean difference for Q4 vs. Q1 (95% CI)	13	0.5–260 (range)	2.3 (−2.8, 6.0)
DEP (measured by MEP)					
Meeker et al. (2009); Medium; 425	Ln-transformed exposure and outcome (except testosterone)	β (95% CI) for IQR increase	153	59.9–518	8.87 (−7.18, 24.9)
Jurewicz et al. (2013); Medium; 269	Log-transformed exposure	β (p)	45	3.8–2,483 (range)	0.08 (p = 0.6)
Den Hond et al. (2015); Low; 120	Ln-transformed exposure	β ± SE	50	20.5–110.5	0.01 ± 0.02
Chang et al. (2015); Low; 176	Ln-transformed exposure and outcome	β (95% CI) for IQR increase₸	13 (fertile mean)		1.00 (0.97, 1.04)
Wang et al. (2015c); Medium; 1,040	Ln-transformed exposure and outcome	% difference (95% CI) 1 unit increase	18	7.1−25	−1.7% (−3.8, 0.30)
Meeker and Ferguson (2014); Medium; 160 (12–19 yr)	None reported	% change (95% CI) with IQR increase	26	14.0−46.9	9.46 (−17.1, 44.5)
267 (20–40 yr)			27	12.2−74.7	−3.30 (−9.81, 3.67)
(Pan et al., 2016); Pan et al. (2015); Medium; 1,066	Ln-transformed exposure and outcome	% change (CI)	13	6.6–32	−1.5% (−4.0,1.1)

Reference; Study confidence; N	Transformation	Effect estimate	Metabolite (ng/mL) [median unless otherwise specified]	Exposure IQR (or as specified)	Testosterone effect estimate
Axelsson et al. (2015a); Medium; 314	Ln-transformed exposure and outcome	Mean difference for Q4 vs. Q1 (95% CI)	41	2−6,900 (range)	1.0 (−7.9, 11)
Han et al. (2014); Medium; 232	None reported	Partial correlation coefficient	3.1	0.0−59.7 (5^{th}–95^{th})	−0.01

* $p < 0.05$, results that support an association are shaded. Dark gray represents one or more of the following: $p < 0.05$, large effect size (e.g., OR ≥ 1.5, β ≥ −0.5, % difference ≥ 1.0%), or exposure-response trend across categories of exposure. Light gray represents other supportive results.

Ŧ Coefficient was calculated by study authors with back-transformation of both hormone and phthalate metabolite concentrations. A coefficient < 1.0 indicates a multiplicative decrease in hormone level for an IQR change in exposure.

Units for testosterone differed across studies: ng/mL (Jurewicz et al., 2013, Meeker and Ferguson, 2014), nmol/L (Han et al., 2014, Axelsson et al., 2015a, 2015b, Chang et al., 2015, Pan et al., 2015), nmol/mL (Specht et al., 2014), pg/mL (Pan et al., 2006), ng/dL (Meeker et al., 2009, Den Hond et al., 2015, Wang et al., 2015a, 2015b, 2015c).

Table 17

Evidence profile table for male reproductive effects of DEHP.

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
Anogenital distance	Medium confidence Bornehag et al., 2015 (C) Jensen et al., 2016 (C) Swan et al., 2015 (C) Low confidence Bustamante-Montes et al., 2013 (C) Suzuki et al., 2012 (C) Swan, 2008 (C)	Among medium confidence studies: • Consistency • Exposure-response gradient across studies • Minimal concerns for bias Overall: • finding is consistent with other systematic review/meta-analysis (National Academies of Sciences, Engineering, and Medicine, 2017)	• Low precision in Bornehag et al., 2015	Inverse associations between DEHP exposure and anogenital distance reported in 5/6 studies (Jensen et al., 2016, Swan et al., 2015, Bornehag et al., 2015, Swan, 2008, Suzuki et al., 2012), of which 2 were statistically significant (Swan et al., 2015, Swan, 2008). Among 3 medium confidence studies, effect size increased with increasing exposure levels (Fig. 2).	⊕⊕◯ MODERATE	⊕⊕⊕ ROBUST Supported by coherence across outcomes.
Semen parameters	Medium confidence Axelsson et al., 2015a, 2015b (CS) Bloom et al., 2015 (C) Han et al., 2014 (CS) Hauser et al., 2006 (CS) Huang et al., 2013 (CS) Jurewicz et al., 2013 (CS) Liu et al., 2012 (CS) Pan et al., 2015 (CS) Specht et al., 2014 (CS) Thurston et al., 2016 (CS) Wang et al., 2015a, 2015b, 2015c (CS) Wirth et al., 2008 (CS) Low confidence Den Hond et al., 2015 (CS) Herr et al., 2009 (CS)	• Minimal concerns for bias • Biological plausibility • Lower study sensitivity could account for most observed inconsistency (i.e., null results in some studies)	• Difficult to assess exposure-response gradient and precision across studies due to differing analyses/ presentation of results	Inverse associations between DEHP exposure and sperm concentration in 7/14 studies (Herr et al., 2009, Huang et al., 2011, Wirth et al., 2008, Specht et al., 2014, Bloom et al., 2015, Hauser et al., 2006), of which 1 was statistically significant (Bloom et al., 2015). Four studies reported an inverse association with motility (Axelsson et al., 2015a; Huang et al., 2013; Huang et al., 2011, and Jurewicz et al., 2013), and 2 were statistically significant (Axelsson et al., 2015a; Jurewicz et al., 2013) (Table 4). Biological plausibility-Studies showed increased apoptosis (Huang et al., 2014); (Wang et al., 2016b; You et al., 2015), increased reactive oxygen species generation (Huang et al., 2014), and increased sperm aneuploidy	⊕⊕◯ MODERATE for concentration	

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
				(Jurewicz et al., 2013) with increased exposure.		
Testosterone	Medium confidence Axelsson et al., 2015a, 2015b (CS) Han et al., 2014 (CS) Jurewicz et al., 2013 (CS) Meeker and Ferguson, 2014 (CS) Meeker et al., 2009 (CS) Mendiola et al., 2011 (C) Pan et al., 2015 (CS) Specht et al., 2014 (CS) Wang et al., 2015c (CS) Low confidence Chang et al. (2015) (CS) Den Hond et al., 2015 (CS) Pan et al., 2006 (CS) Park et al., 2010 (CS)	• Minimal concerns for bias overall • Risk of bias in low confidence studies and lower study sensitivity account for most observed inconsistency • Exposure-response gradient within one study	• Difficult to assess exposure-response gradient and precision across studies due to differing analyses/ presentation of results	Inverse associations between DEHP exposure and testosterone levels in 8/13 studies (Specht et al., 2014, Meeker and Ferguson, 2014, Wang et al., 2015b, Meeker et al., 2009, Axelsson et al., 2015a, Park et al., 2010, Jurewicz et al., 2013, Pan et al., 2015), 2 of which were statistically significant (Specht et al., 2014, Jurewicz et al., 2013), with the former showing an exposure-response trend, other studies did not examine exposure-response gradient (Table 13).	⊕⊕◯ MODERATE	
	Time to Pregnancy				⊕◯◯ SLIGHT	
	Hypospadias/cryptorchidism and pubertal development				◯◯◯ INDETERMINATE	

C: cohort, CC: case-control, CS: cross-sectional.

Table 18

Evidence profile table for male reproductive effects of DINP.

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
Testosterone	Medium confidence Axelsson et al., 2015a, 2015b (CS) Jurewicz et al., 2013 (CS) Meeker and Ferguson, 2014 (CS) Pan et al., 2015 (CS) Specht et al., 2014 (CS)	• Minimal concerns for bias • Large effect size in one study (23% decrease with iqr increase in exposure) • Exposure-response gradient within one study	• Some unexplained inconsistency	Inverse associations between DINP exposure and testosterone levels in 3/5 studies (Specht et al., 2014, Meeker and Ferguson, 2014, Pan et al., 2015), 2 included statistically significant results (Pan et al., 2015, Specht et al., 2014), with the latter being a trend (other studies did not examine exposure-response gradient) (Table 14).	⊕⊕◯ MODERATE	⊕⊕◯ MODERATE Based on testosterone and semen parameters, supported by coherence of slight findings in other outcomes with few available studies
Semen parameters	Medium confidence Axelsson et al., 2015a, 2015b (CS) Jurewicz et al., 2013 (CS) (Pan et al., 2015) (CS) Specht et al., 2014 (CS)	• Minimal concerns for bias • Exposure-response gradient within one study • Consistency for morphology	• Some unexplained inconsistency for concentration	Inverse associations between DINP exposure and sperm morphology in all 4 studies, 1 of which was statistically significant (Jurewicz et al., 2013). 2/3 studies for motility (Pan et al., 2015, Axelsson et al., 2015a) and 2/4 studies for concentration (Specht et al., 2014, Pan et al., 2015) also reported inverse associations (Table 5).	⊕⊕◯ MODERATE	
Anogenital distance, Hypospadias/ Cryptorchidism					⊕◯◯ SLIGHT	
Time to pregnancy, pubertal development					◯◯◯ INDETERMINATE	

C: cohort, CC: case-control, CS: cross-sectional.

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Table 19

Evidence profile table for male reproductive effects of DBP.

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
Semen parameters	Medium confidence Axelsson et al., 2015a, 2015b (CS) Bloom et al., 2015 (C) Han et al., 2014 (CS) Hauser et al., 2006 (CS) Jonsson et al., 2005 (CS) Jurewicz et al., 2013 (CS) Liu et al., 2012 (CS) Pan et al., 2015 (CS) Thurston et al., 2016 (CS) Wang et al., 2015c (CS) Wirth et al., 2008 (CS) Low confidence Den Hond et al., 2015 (CS)	• Minimal concerns for bias • Consistency for concentration • Biological plausibility • Exposure-response gradient within three studies	• Difficult to assess exposure-response gradient and precision across studies due to differing analyses/ presentation of results	Inverse associations between DBP exposure and sperm concentration in 8/12 studies (Bloom et al., 2015; Jurewicz et al., 2013; Wang et al., 2015a, 2015b, 2015c; Pan et al., 2015; Jonsson et al., 2005; Hauser et al., 2006; Han et al., 2014; Liu et al., 2012), of which 3 were statistically significant and displayed monotonic exposure-response relationships (Wang et al., 2015a; Liu et al., 2012; Hauser et al., 2006). Seven studies reported an inverse association with motility (Wang et al., 2015a, 2015b, 2015c; Bloom et al., 2015; Thurston et al., 2016; Jurewicz et al., 2013; Pan et al., 2015; Axelsson et al., 2015a, 2015b; Hauser et al., 2006), and 2 were statistically significant (Axelsson et al., 2015a; Hauser et al., 2006) (Table 6) Biological plausibility-Studies showed increased sperm aneuploidy (Jurewicz et al., 2013) with increased exposure.	⊕⊕⊕ ROBUST for concentration	⊕⊕⊕ ROBUST Based on semen parameters, supported by coherence across outcomes.
Anogenital distance	Medium confidence Bornehag et al., 2015 (C) Jensen et al., 2016 (C) Swan et al., 2015 (C) Low confidence Suzuki et al., 2012 (C) Swan, 2008 (C)	• Findings largely consistent • Minimal concerns for bias • Finding is consistent with other systematic review/ meta-analysis (National Academies of Sciences, Engineering, and Medicine, 2017)	• Low precision in Bornehag et al., 2015	Inverse associations between DBP exposure and anogenital distance reported in 3/5 studies (Swan et al., 2015, Bornehag et al., 2015, Swan, 2008), of which Swan, 2008 was statistically significant (Fig. 2-C).	⊕⊕◯ MODERATE	
Time to pregnancy	High confidence Buck Louis et al., 2014 (C)	• Study well conducted	• Single study	Decrease in fecundability with increased DBP exposure in one study (Buck Louis et al., 2014);	⊕⊕◯ MODERATE	

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
		• Large effect size (fecundability OR = 0.82)		results were statistically significant (Table 11).		
Hypospadias/ cryptorchidism, testosterone					⊕◯◯ SLIGHT	
Pubertal development					◯◯◯ INDETERMINATE	

C: cohort, CC: case-control, CS: cross-sectional, OR = odds ratio.

Table 20

Evidence profile table for male reproductive effects of DIBP.

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
Testosterone	Medium confidence Meeker and Ferguson, 2014 (CS) Pan et al., 2015 (CS) Low confidence Chang et al., 2015 (CS) Den Hond et al., 2015 (CS)	• Consistency • Minimal risk of bias in medium confidence studies	• Few studies available • Association in one study only observed in adolescents	Inverse associations between DIBP exposure and testosterone levels in 3/4 studies (Meeker and Ferguson, 2014, Pan et al., 2015, Chang et al., 2015), 2 of which were statistically significant. No studies examined exposure-response gradient (Table 15).	⊕⊕◯ MODERATE	⊕⊕◯ MODERATE Based on testosterone and supported by *slight* evidence in other outcomes, with explanation for weaker observed associations (i.e., sensitivity and few available studies). Results for DBP, a structurally similar phthalate are also supportive.
Anogenital distance, semen parameters, time to pregnancy hypospadias/ cryptorchidism					⊕◯◯ SLIGHT	
Pubertal development					◯◯◯ INDETERMINATE	

C: cohort, CC: case-control, CS: cross-sectional.

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Table 21

Evidence profile table for male reproductive effects of BBP.

Outcome	Studies (design in parentheses)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Confidence judgement for outcome	Confidence judgement for overall hazard
Semen parameters	Medium confidence Axelsson et al., 2015a, 2015b (CS) Bloom et al., 2015 (CS) Hauser et al., 2006 (CS) Jonsson et al., 2005 (CS) Jurewicz et al., 2013 (CS) Pan et al., 2015 (CS) Thurston et al., 2016 (CS) Wang et al., 2015c (CS) Wirth et al., 2008 (CS) Low confidence Den Hond et al., 2015 (CS)	• Minimal concerns for bias • Lower study sensitivity could account for most observed inconsistency for motility • Biological plausibility	• Difficult to assess exposure-response gradient and precision across studies due to differing analyses/ presentation of results	Inverse associations between BBP exposure and sperm concentration in 4/10 studies (Bloom et al., 2015; Hauser et al., 2006; Wirth et al., 2008; Pan et al., 2015), of which 2 were statistically significant (Bloom et al., 2015; Pan et al., 2015). Eight studies reported an inverse association with motility (Bloom et al., 2015; Den Hond et al., 2015; Hauser et al., 2006; Axelsson et al., 2015a; Jonsson et al., 2005; Wirth et al., 2008; Pan et al., 2015; Thurston et al., 2016), and 1 was statistically significant (Thurston et al., 2016) (Table 8). Biological plausibility- Studies showed increased sperm aneuploidy (Jurewicz et al., 2013) with increased exposure.	⊕⊕◯ MODERATE for motility	⊕⊕◯ MODERATE Supported by coherence across outcomes.
Time to pregnancy	High confidence Buck Louis et al., 2014 (C)	• Study well conducted • Large effect size (fecundability OR = 0.77)	• Single study	Decrease in fecundability with increased BBP exposure in one study (Buck Louis et al., 2014); results were statistically significant (Table 11).	⊕⊕◯ MODERATE	
Anogenital distance, hypospadias/ cryptorchidism					⊕◯◯ SLIGHT	
Testosterone, pubertal development					◯◯◯ INDETERMINATE	

C: cohort, CC: case-control, CS: cross-sectional, OR = odds ratio.