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## Phthalate exposure and metabolic effects: 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 metabolic 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 metabolic effects in humans, and outcomes were selected for full systematic review based on data availability.

**Study evaluation and synthesis methods:** Studies of diabetes and insulin resistance were evaluated using criteria defined a priori for risk of bias and sensitivity by two reviewers using a domain-based approach; studies identified with a pre-defined critical deficiency were excluded. Evidence was synthesized by outcome and phthalate and strength of evidence was summarized using a structured framework. Studies of obesity and renal effects received “screening level” reviews to determine whether full systematic review was warranted.

**Results:** The primary outcomes reviewed here are (number of included/excluded studies in parentheses): type 2 diabetes (1/3), insulin resistance (13/3), and impaired glucose tolerance and blood glucose in pregnancy (4/2). For DEHP exposure, there was consistency among studies of insulin resistance and coherence with the single included study of diabetes, as well as an observed exposure-response gradient observed in a study of insulin resistance. This evidence is considered moderate. Similarly, for DBP and DIBP exposure, the evidence is considered moderate due to strong positive associations in the diabetes study and coherent results for insulin resistance. For DINP, BBP, and DEP, the evidence is considered slight. No association was reported in the single study of diabetes with BBP and DEP exposure (DINP was not investigated). The available evidence does indicate an association between exposure to these phthalates and insulin resistance, but the small number of studies and the lack of coherence with diabetes decreases confidence.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.04.040>.

The screening level reviews for obesity and renal effects determined that the currently available evidence is inadequate to assess the associations between these outcomes and phthalate exposure.

**Conclusions and implications of key findings:** Overall, these results support that phthalate exposure at levels seen in human populations may have metabolic effects. Given the mechanistic support, the large effect sizes for incident diabetes in the single available study, and the coherence with insulin resistance, the association between phthalate exposure and diabetes risk should be considered when assessing the risks and costs of exposure to specific phthalates in humans.

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

## 1. Introduction

Human exposure to phthalates (manmade phthalic acid diesters) is ubiquitous because of the widespread use of these chemicals in consumer and industrial products. These compounds have a variety of different structures and properties that determine their uses. Phthalates are used in polyvinyl chloride products and in some medications and personal care products. In general, these diesters are rapidly metabolized to monoester metabolites and are excreted in the urine. Endocrine, and endocrine-disruption, effects on metabolism and on metabolic diseases is a growing area of research with significant public health implications (Heindel et al., 2017). This review focuses on studies of phthalate exposure and metabolic-related outcomes.

The phthalates evaluated in 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). 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 (NAS 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.

Past reviews examined the association between phthalates and diabetes and obesity and found the evidence inadequate to conclude whether an association existed (Kuo et al., 2013; Thayer et al., 2012). However, additional studies have been published in the interim, and no systematic review is available on insulin resistance, an emerging area of research in the phthalate literature. As part of a comprehensive evaluation of the epidemiological literature on phthalates, we performed a systematic review on the association between phthalate exposure and metabolic effects, specifically diabetes, insulin resistance, and obesity. We also examined renal effects because they can be a long-term complication of diabetes and because impaired renal function could affect interpretation of exposure measures based on urinary concentrations of phthalate metabolites (Table 1). We focus on Type 2 diabetes, which is characterized by insulin resistance and the resulting insulin deficiency due to the inability of the pancreas to produce enough insulin. Obesity is a strong risk factor for Type 2 diabetes, and the highest incidence of Type 2 diabetes is in middle- and older-aged adults. In contrast, Type 1 diabetes involves a different etiology, an autoimmune-mediated destruction

of the pancreatic islets of Langerhans cells. Incidence of Type 1 diabetes is highest in children and teenagers.

To make the systematic review more pragmatic, so that limited resources were not utilized to assess bodies of evidence that would likely be inadequate for reaching conclusions about the association, obesity and renal effects received less robust “screening level” reviews to determine the extent and nature of the literature for evidence synthesis. This approach is consistent with recommendations from the National Academies of Science encouraging the U.S. Environmental Protection Agency to explore ways to make systematic review more feasible, including a “rapid review in which components of the systematic review process are simplified or omitted (e.g., the need for two independent reviewers)” (National Academy of Sciences, 2017).

## 2. Methods

The full methods for this systematic review, including for literature search and screening, study evaluation, data extraction, and evidence synthesis are described in detail in the protocol (Supplemental materials). An abbreviated version is provided below, with references to specific sections of the protocol for ease of reference. In addition, the key tables from the protocol that are necessary to understand how conclusions were reached are included in a separate supplemental file (key methods supplement).

### 2.1. Literature search and screening

Epidemiology studies were identified by conducting a single broad literature search on all six phthalates of interest (DEHP, DINP, DBP, DIBP, BBP, DEP). The Population, Exposure, Comparators, and Outcome (PECO) criteria are available in the protocol (Section 2.2). The following databases were searched: PubMed, Web of Science, and Toxline, with the initial search in 2013, and updates every 6–12 months through August 2018 (protocol Section 3). Forward and backward searches were also performed. Title/abstract and full text screening was performed by two reviewers.

### 2.2. Study evaluation

Study evaluation (protocol Section 4.1) was conducted by two reviewers for those outcomes receiving full systematic review (i.e., diabetes, insulin resistance, gestational diabetes). 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). Evaluation was conducted for the following domains: exposure measurement, outcome ascertainment, participant selection, confounding, analysis, sensitivity, and selective reporting. These domains were based on the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016), modified for use with environmental exposures. Phthalate and outcome-specific criteria were developed prior to evaluation and are described briefly below. Detailed exposure criteria are available in the key methods supplement and the protocol (Section 4.1.1). Detailed outcome-specific evaluation criteria are available in the supplement and summarized briefly below.

For evaluating 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 greater reliability of single biomarker 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). This critical deficiency was used as a basis for excluding studies from subsequent analyses.

Several outcome-specific criteria were applied across multiple evaluation domains (for more details, see outcome-specific criteria in the supplement). Timing of exposure measurement was an important consideration, particularly given the short half-life of phthalates (3–18 h for phthalate metabolites in a review by Johns et al. (2015)). For diabetes, it is important for studies to exclude individuals with diabetes at baseline and include only individuals with incident disease as cases, with exposure measured prior to development of diabetes in order to establish their temporality. Accordingly, studies of diabetes with exposure measured concurrent with the outcome were excluded, and prospective designs were generally needed for inclusion. For insulin resistance, it is appropriate to measure the exposure and outcome concurrently as the outcome can be a short-term response. Several criteria for outcome ascertainment were also applied. For diabetes, to identify undiagnosed cases, the use of the American Diabetes Association definition with information about required fasting, laboratory test requirements and assays, quality control procedures, and reliability or validity measures were preferred, while self-reported physician diagnosis or medical treatment for diabetes was appropriate for diagnosed cases. For insulin resistance, diabetics must be excluded as measures of insulin are not interpretable in the presence of diabetes, especially if diabetes is treated with hypoglycemic medication, as treatment will influence insulin production and secretion. In addition, fasting insulin and/or glucose measurements were required, and information on testing as described for diabetes was preferred. HOMA-IR was used as the primary measure of insulin resistance when available. In evaluating confounding, the following risk factors were considered possible confounders: age, gender, adiposity/body mass index, lifestyle (physical inactivity, poor diet, smoking, heavy alcohol consumption), and socioeconomic status. It was not required that a study adjusts for all of these variables; rather, the study evaluation considered whether omission of these covariates was likely to have introduced bias into the effect estimates. There is also potential for confounding across the phthalates, particularly when results are similar for two moderately (or higher) correlated phthalates in a study. Study evaluations were not downgraded due to this potential, but it was considered during evidence synthesis as another source of uncertainty in the results.

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 considered together to reach an overall study confidence classification of *High*, *Medium*, *Low*, or *Uninformative*. This overall classification was not based on pre-defined weights of the domains, but rather was based on reviewer judgments, and includes the likely impact the noted deficiencies in bias

and sensitivity have on the results, which varies depending on the study and/or outcome. 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 (Section 4) and the key methods supplement. Study evaluations were documented in Health Assessment Workspace (HAWC), and ratings and the rationales are available at links provided in the results.

### 2.3. Evidence synthesis

After study evaluation, the evidence for each outcome was synthesized separately for each phthalate using a structured framework, using the following aspects of an association that may support causation: consistency, exposure-response relationship, strength of association, temporal relationship, biological plausibility, and coherence. In evaluating the evidence for each of these considerations, syntheses also consider study evaluation decisions, with high confidence studies carrying the most weight and consideration of specific strengths and limitations of individual studies described. 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 for which uncertainties prevent drawing a causal conclusion in either direction. 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 diabetes risk (encompassing incident diabetes and insulin resistance) for each phthalate, using a structured framework available in the key methods supplement and the protocol (Section 6). This structured framework is conceptually similar to and is informed by the well-established Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (Schünemann et al., 2013), but is designed to address the challenges specific to the analysis of environmental health data rather than clinical evidence. No statistical quantitative meta-analysis was performed due to substantial differences across studies.

For obesity and renal disease, screening-level reviews were conducted to determine whether new literature suggest full systematic reviews would be warranted and to identify key research gaps. One reviewer identified studies that should be excluded based on exposure assessment and temporality. The remaining studies were then each evaluated by a single reviewer and were assessed for consistency, while considering whether any observed inconsistency could potentially be attributed to differences in study confidence or exposure level. If this screening level review indicated little consistency among studies, with no clear explanation based on study confidence, then full data extraction and additional evidence analysis and synthesis was not pursued, and the evidence was considered inadequate. The screening level reviews should not be considered as substitutes for systematic review.

Reporting of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The work described herein was federally funded.

### 3. Results

The literature flow diagram, depicting the identification and disposition of the literature search records, is shown in Fig. 1. A list of all the studies identified in the search that met the PECO criteria is available in the supplement. For each outcome, the included and excluded studies are described in the respective section within the text.

#### 3.1. Type 2 diabetes

**3.1.1. Study selection and evaluation**—Based on evaluation of temporality, six of the seven epidemiology studies identified in the search with data on type 2 diabetes were excluded because exposure was measured at the same time as ascertainment of diabetes status. One study (Sun et al., 2014), a nested case-control study within two cohorts (Nurses' Health Study (NHS) and NHSII), was identified in the search as having prospective data on diabetes risk. The specific phthalates examined in that study and the evaluation are summarized in Table 2; this study was classified as *medium* confidence and rationales are available in HAWC at <https://hawcprd.epa.gov/rob/study/100000200/>.

**3.1.2. Results**—In Sun et al. (2014), there were statistically significant strong positive associations between increased exposure to DBP and DIBP and diabetes risk (Table 3), however pooled results were not available and the positive associations were observed only in participants from NHSII, which is a more homogenous and younger cohort (mean age = 46 vs. 66) with higher exposure levels. In addition, the association was stronger when adjusting for BMI. It is possible that adiposity could lie on the causal pathway between phthalate exposure and diabetes risk, and this should be considered when interpreting the effect estimates. Results were similar for DEHP, but the positive association was smaller and not statistically significant. For BBP and DEP, no association was reported, and no results were available for DINP, so the evidence for these three phthalates is considered indeterminate.

#### 3.2. Insulin resistance

**3.2.1. Study selection and evaluation**—Three of the 21 publications identified in the search with data on insulin resistance were excluded due to exposure measurement in tissue other than urine or other critical deficiencies. Of the remaining 18 publications, six were based on data from the National Health and Nutrition Examination Survey (NHANES), with different samples but overlapping populations in many. Among the NHANES analyses in adults, one was selected as the primary study (Huang et al., 2014) and the results of the others were reviewed for discrepancies in methods or results. Two NHANES analyses in adolescents did not have overlapping years and were included separately in the review of data in adolescents (Trasande et al., 2013; Attina and Trasande, 2015). Thus, there were a total of 13 studies in the review. The specific phthalates examined in these included studies

and the evaluations are summarized in Table 4. Rationales for ratings are available at: <https://hawcprd.epa.gov/summary/visual/100000076/>.

In adults, there were seven studies, including six cross-sectional (Chen et al., 2017; Dales et al., 2018; Dirinck et al., 2015; Huang et al., 2014; Hong et al., 2009; Hong et al., 2016) and one cohort (Kim and Hong, 2014). Three studies reported on adolescents (Chen et al., 2017; Trasande et al., 2013; Attina and Trasande, 2015) and four studies reported on children (Carlsson et al., 2018; Kataria et al., 2017; Saengkaew et al., 2017; Watkins et al., 2016). All used a single urine sample to measure exposure, with the exception of Kim et al. (2013), which collected samples at up to five visits. Eight studies (Chen et al., 2017; Dales et al., 2018; Huang et al., 2014; Hong et al., 2016; Kim and Hong, 2014; Trasande et al., 2013; Attina and Trasande, 2015; Watkins et al., 2016) were classified as medium confidence and the remaining five were classified as low confidence. This set of studies as a whole would be improved with additional studies with repeated exposure measures, and with prospective rather than cross-sectional data collection. However, the strengths of these studies include the wide variety of populations and the availability of data from multiple nationally representative samples, which have large sample sizes and are expected to represent the general population.

**3.2.2. Results and synthesis—**The majority of available studies examined adult and/or adolescent exposure with concurrent measures of insulin resistance (or repeated measures in the case of Kim et al. (2013)), so these are the focus of this review. Three of the four studies in children were classified as low confidence and the fourth study (Watkins et al., 2016) used an in-utero exposure measure which may not be comparable to the other studies, so results in children are briefly summarized in text only.

Evaluation of the evidence of an association between exposure to DEHP and insulin resistance in adults is based on seven studies (Table 5). Five studies, including four of the five medium confidence studies, reported higher glucose, insulin, and HOMA-IR with higher exposure levels. Results were statistically significant for at least one outcome in four studies and exposure-response gradients were observed for all three outcomes in Huang et al., 2014. However, there is some uncertainty resulting from study limitations. The positive result in Kim et al. (2013) is difficult to interpret because the analysis included subjects with a history of diabetes diagnosis, though this is ameliorated to some extent by an analysis in women adjusting for history of DM and showing consistent results. Additionally, the results in Dirinck et al. (2015) should be interpreted with caution due to the study evaluation concerns. The fact that the latter study had the highest effect estimates could possibly be explained by selection bias, by the specific population (obese patients), or some other factor. In addition, there is potential for residual confounding by diet, but the impact of this is uncertain. While two studies (Huang et al. (2014); Kim et al. (2013)) adjusted for caloric intake, this may not be adequate to adjust for differing exposure levels by food type (e.g., packaged foods). This issue is considered further in the discussion. Despite these limitations, the overall consistency in the direction of the association across studies and the exposure-response gradient observed in a well-conducted and sensitive study increase confidence in the association. In adolescents, only one of the three studies reported higher insulin

resistance with higher exposure. The three studies in children found no clear association (Watkins et al., 2016; Carlsson et al., 2018; Kataria et al., 2017).

One medium confidence study included results on the association between DINP and insulin resistance. Attina and Trasande (2015), an NHANES sample of adolescents, reported increased HOMA-IR levels with increasing exposure, with the third tertile being statistically significant ( $\beta$  for tertile 2: 0.07 (−0.09, 0.22), tertile 3: 0.23 (0.08, 0.38)). In addition, one low confidence study in children (Kataria et al., 2017) reported no significant association, but did not report quantitative estimates.

Evaluation of the evidence of an association between exposure to DBP and insulin resistance in adults is based on seven studies (Table 6). Four studies, including three of the five medium confidence studies (Table 6) reported increased glucose, insulin, and/or HOMA-IR. Results in two of these studies were statistically significant, and an exposure-response gradient was observed for glucose and HOMA-IR in Huang et al. (2014). However, in Dales et al. (2018), a weak association was only observed for insulin. Further, as with DEHP, the positive results in Kim et al. (2013) and Dirinck et al. (2015) are difficult to interpret, and there is potential for residual confounding by diet. The other studies reported no association, resulting in some unexplained inconsistency, including between NHANES and CHMS, the nationally representative surveys for fasting glucose and HOMA-IR. This lack of consistency decreases confidence in the association since there is no clear explanation such as study sensitivity (e.g., exposure levels or range) for the differing results. In adolescents, one of the three studies reported higher insulin resistance with higher exposure (Trasande et al., 2013). The three studies in children (Watkins et al., 2016) found no clear association, though there was a statistically significant increase in fasting glucose among pubertal girls based on peripubertal exposure in Watkins et al. (2016) for summed MBP + MIBP.

Three studies reported results on the association between DIBP exposure and insulin resistance in adults (Table 7). One of two medium confidence studies and one low confidence study reported higher glucose, insulin, and HOMA-IR with higher exposure, with Huang et al. (2014) reporting statistical significance for HOMA-IR and exposure-response gradients for glucose and HOMA-IR. However, as with DBP, there was inconsistency between the nationally representative surveys with no clear explanation and the results from Dirinck et al. (2015) have low confidence, and the small number of studies makes evaluating consistency a challenge. As with the other phthalates, there is potential for residual confounding by diet. In adolescents, one of the two studies reported higher insulin resistance with higher exposure (Trasande et al., 2013). Results for BBP (Table 8) and DEP (Table 9) were similar to those of DIBP, though there was no association in adolescents for these phthalates. The studies in children (Watkins et al., 2016) found no clear association for BBP and DEP, though there was a statistically significant increase in fasting glucose among pubertal girls based on peripubertal exposure for DEP.

Overall, across the phthalates, there is generally a stronger association in adults than adolescents and children. Because there was a smaller number of studies of the younger age groups, and there were limitations in the studies that are available, including a lack of exposure information, it is unclear whether this is a true difference and whether it can



be explained by changing exposure levels, biological factors, or some other explanation. In addition to the main effects described above, some of the analyses of NHANES data examined differences in the association by sub-population. In Huang et al. (2014), these factors did not generally change the direction of association, but there were differences in strength of association by race/ethnicity and sex. For some phthalates, the association was stronger in black and Hispanic people than in whites. The sex with the stronger association differed by phthalate. Since there were no additional studies that examined these differences, there was limited ability to draw conclusions about the interactions.

### 3.3. Gestational diabetes

**3.3.1. Study selection and evaluation**—Two of the six epidemiology studies identified in the search with data on diabetes and/or insulin resistance during pregnancy were excluded due to exposure measurement in tissue other than urine or unavailability in full text. The specific phthalates examined in the remaining four included studies and the evaluations are summarized in Table 10. Rationales for ratings are available at: <https://hawcprd.epa.gov/summary/visual/100500026/>. All four studies were pregnancy cohorts, with exposure measurement during pregnancy. Two studies collected more than one urine sample (James-Todd et al., 2016b; James-Todd et al., 2018). One study was considered high confidence (James-Todd et al., 2018), two medium confidence (James-Todd et al., 2016b; Shapiro et al., 2015), and one low confidence (Robledo et al., 2015). Looking across the studies, this set of cohorts is generally well-conducted with low risk of bias, but the exposure levels trend slightly lower than in other studies, so sensitivity to observe an effect may be lower.

**3.3.2. Results and synthesis**—Among the four studies that examined blood glucose and/or impaired glucose tolerance in pregnant women, there was no clear indication of an increase in blood glucose with increased phthalate exposure for DEHP (Table 11), DBP, and DIBP (Table 12). For BBP (Table 13), there were two studies indicating higher blood glucose or impaired glucose tolerance with higher exposure, but neither was statistically significant (James-Todd et al., 2016b; Shapiro et al., 2015). For DEP (Table 13), two studies reported statistically significant associations (James-Todd et al. (2018) for blood glucose and James-Todd et al. (2016b) for impaired glucose tolerance), but the other two studies reported no association. Across the phthalates, with the exception of DEP, the high confidence study (James-Todd et al., 2018) reported no association. This could be due to the lower exposure levels in the study population, which may have reduced study sensitivity.

### 3.4. Diabetes risk summary

For each phthalate, Table 14 presents a summary of the key factors that increased or decreased confidence in the evidence, a summary of the findings, and an overall judgment of the strength of evidence that considers coherence across the two main outcomes (i.e., type 2 diabetes and insulin resistance), focusing on the studies in adults. For DEHP exposure, there was consistency and an exposure-response gradient in one study for insulin resistance and coherence across diabetes and insulin resistance, though the results for diabetes were not statistically significant. Given the overall consistency, but some lingering uncertainty in the evidence, this evidence is considered moderate.

For DBP and DIBP exposure, in contrast, the overall evidence is considered moderate primarily due to the strong positive associations in the single diabetes study. There is substantial unexplained inconsistency in the results for insulin resistance, but some of the results, including exposure-response gradients in one well-conducted study, provide coherence with the incident diabetes results.

For DINP, BBP, and DEP, the evidence is considered slight. No association was reported in the single study of diabetes with BBP and DEP exposure (DINP was not investigated). The available evidence does indicate an association between exposure to these phthalates and insulin resistance, including in pregnant women, but the small number of studies and the lack of coherence with diabetes decreases confidence.

### 3.5. Obesity

A prior review concluded that the data on obesity and phthalate exposure is inconsistent (Thayer et al., 2012). We conducted a screening level review encompassing these and more recent studies. Twenty-five of the 32 epidemiology studies (described in 35 publications) identified in the search with data on obesity or BMI were excluded (Supplementary Table). The majority were excluded due to issues with temporality (i.e., exposure was measured at the same time as BMI), or due to measurement of exposure in tissues other than urine. Six of the remaining studies focused on obesity in children or infants based on prenatal or childhood exposure. The screening level review of these studies indicated little consistency with no clear explanation based on a preliminary evaluation of study confidence or exposure levels (Supplementary Table). Therefore, a full systematic review was not performed and the evidence is considered inadequate.

Along among the included studies was a single prospective study of adult weight gain (Song et al., 2014), which used the controls from the nested case-control study on type 2 diabetes described previously (Sun et al., 2014) and measured weight gain over ten years. For summed DBP + DIBP and BBP, there were statistically significant associations between increased exposure and weight gain, with exposure-response gradients observed. For DEHP and DEP, no association was observed, and no results were available for DINP. Since the effect sizes for the positive associations were small (approximately 0.3 kg per year) and there is potential for residual confounding by diet (as described for diabetes), the evidence from a single study is considered inadequate to draw a conclusion about the association with obesity.

### 3.6. Renal effects

Five epidemiology studies examined the association between phthalate exposure and renal effects. Three studies were excluded due to critical deficiencies in exposure measurement (Supplementary Table). Both of the remaining studies were considered to be low confidence by a single reviewer due to selection bias (Tsai et al. (2016) or possible reverse causation (Trasande et al. (2014). Because of inconsistency in the results and the availability of only low confidence studies, a full systematic review was not performed, and the evidence is considered inadequate.

## 4. Discussion

Based on screening-level reviews, the currently available evidence was determined to be inadequate to assess associations between obesity and renal effects and phthalate exposure. It is unlikely that a full systematic review of the existing literature would indicate a clear association, either due to a small number of low confidence studies available or disparate results. The use of screening-level reviews allowed us to avoid using additional resources required for a full systematic review for these outcomes at this time. It is important to note, however, that we do not mean to imply that systematic reviews are not useful in situations where the evidence is inconsistent. To the contrary, systematic review may be particularly beneficial for evidence bases with conflicting results because it provides a process for identifying factors that may explain the discrepancies (e.g., study quality, exposure levels). The benefit gained from the review will depend on the context of the review. In this case, the focus was on identifying key hazards of phthalate exposure with a robust database, and there was a need to be pragmatic in the use of resources to conduct the review.

Evidence for an association between phthalate exposure and diabetes risk is more convincing. The single prospective study that examined incident diabetes as an outcome reported strong associations for multiple phthalates, and several studies reported associations with insulin resistance. When coherence across these outcomes was considered, DEHP, DBP, and DIBP had moderate evidence of an association, and DINP, BBP, and DEP had slight evidence of an association (Table 14).

Diet was considered a possible confounder for the observed association with diabetes and obesity. Only a portion of the studies controlled for diet, and those that did used only caloric intake as a proxy. While this would account for increased exposure simply from eating more in general, there may be other diet-related factors associated with phthalate exposure, such as frequent consumption of packaged/processed foods or fatty foods, which may not be fully accounted for with adjustment for caloric intake, and which may carry an additional risk with respect to diabetes (Micha et al., 2010; Franz et al., 2002; Hu et al., 2001). Phthalates, particularly DEHP and DBP, are present in most food-packaging materials (Balafas et al., 1999) and plastic-packaged food products (Cirillo et al., 2013) and can migrate into food (Serrano et al., 2014a; Castle et al., 1994). This migration is increased with microwave heating (Chen et al., 2008). Phthalate levels in different food types have been reviewed previously and meats (particularly poultry) and fats/oils have been consistently associated with increased phthalate exposure (Serrano et al., 2014a). Since the 2014 review, participants in a pre-defined “fatty, sweet, and ready meal” group had higher exposure to DEHP and DBP in one study (Serrano et al., 2014b). Other foods may vary in phthalate levels, based partly on region (Serrano et al., 2014a). A change in diet to fresh, mostly organic meals prepared without plastics in procurement, cooking, and serving has been shown to reduce DEHP exposure (Rudel et al., 2011). Taken as a whole, it is conceivable that individuals who eat a diet higher in packaged, microwaved, and fatty foods may be at higher risk for diabetes and obesity, and this diet may also increase phthalate exposure, though the influence of diet may differ by phthalate. The concern would be highest for DEHP, which is commonly used in packaging and is more associated with fatty foods due to its more lipophilic nature (Cao, 2010). DBP, DIBP, BBP are all used in packaging, though perhaps less so than DEHP (Van

Holderbeke et al., 2014; Fierens et al., 2012), while DEP is not frequently used in packaging and is less likely to contaminate food (Schettler, 2006). The fact that a similar association with insulin resistance was observed for DEP as the other phthalates reduces the concern about residual confounding overall, but given the small evidence base, it is worth further, more detailed exploration of diet as a potential confounder.

As mentioned in the methods, another important source of potential confounding is across phthalates. When drawing conclusions about associations between individual phthalates and health effects, it can be difficult to conclusively determine that the observed associations are not due to confounding across the phthalates. Correlations between some of the phthalates included in this review are moderately high (e.g., DBP, DIBP, BBP metabolites  $r = 0.5$  to  $0.7$  (Johns et al., 2015)), which increases this concern. While some phthalate studies present multi-pollutant models, this is far from universal, and there are also concerns that bias can be amplified in multipollutant regression models (Weisskopf et al., 2018). Thus, this is an area of uncertainty for reviews of phthalates and other chemical mixtures, and is discussed in more detail in a forthcoming special issue editorial. Our ability to assess this type of confounding is somewhat limited by the different sensitivity of the studies for different phthalates (e.g., due to exposure levels), which reduced the ability to assess coherence across phthalates, and by the fact that we might expect more similar phthalates to be both highly correlated with each other and have similar effects (e.g., DBP and DIBP). However, it is unlikely that this issue would significantly alter the conclusions of this review. None of the associations in this review approached the level of “Robust” evidence, where uncertainty is largely eliminated and alternative explanations for the association such as chance, bias, and confounding are ruled out. Still, this is certainly an important issue for phthalate research moving forward. Methods development to address this concern is a rapidly developing field, and researchers should consider the potential for confounding across phthalates in designing their studies and analyzing data. In addition, given that people are exposed to mixtures of chemicals like phthalates, there may be a benefit in some cases to drawing conclusions for mixtures (such as all phthalates or subclasses of phthalates) rather than for individual chemicals, though this is not without its own complications.

An established mechanism for the association between phthalate exposure and diabetes and insulin resistance would also increase confidence in the association despite the possibility of residual confounding. Plausible mechanisms for the association have been described elsewhere. Phthalates can alter peroxisome proliferator-activated receptors (PPARs), which contribute to adipogenesis, lipid metabolism, and metabolic homeostasis (Benjamin et al., 2017a; Watkins et al., 2016; Attina and Trasande, 2015; Sun et al., 2014; Thayer et al., n.d.). Oxidative stress is another possible mechanism (Watkins et al., 2016).

Given the mechanistic plausibility, the large effect sizes for incident diabetes in the single available study for some phthalates, and the coherence with insulin resistance, the association between phthalate exposure and diabetes risk should be considered when assessing the risks and costs of exposure to specific phthalates in humans. This is consistent with findings by Legler et al. (2015) and Benjamin et al. (2017b) in narrative reviews. Additional prospective research with repeated measures of exposure would further clarify the relationship, as would additional high-quality research on the related metabolic effects

(obesity, renal effects) to better understand coherence across outcomes. Discussion of some additional issues that apply to all phthalate studies, is presented in the special issue editorial (forthcoming).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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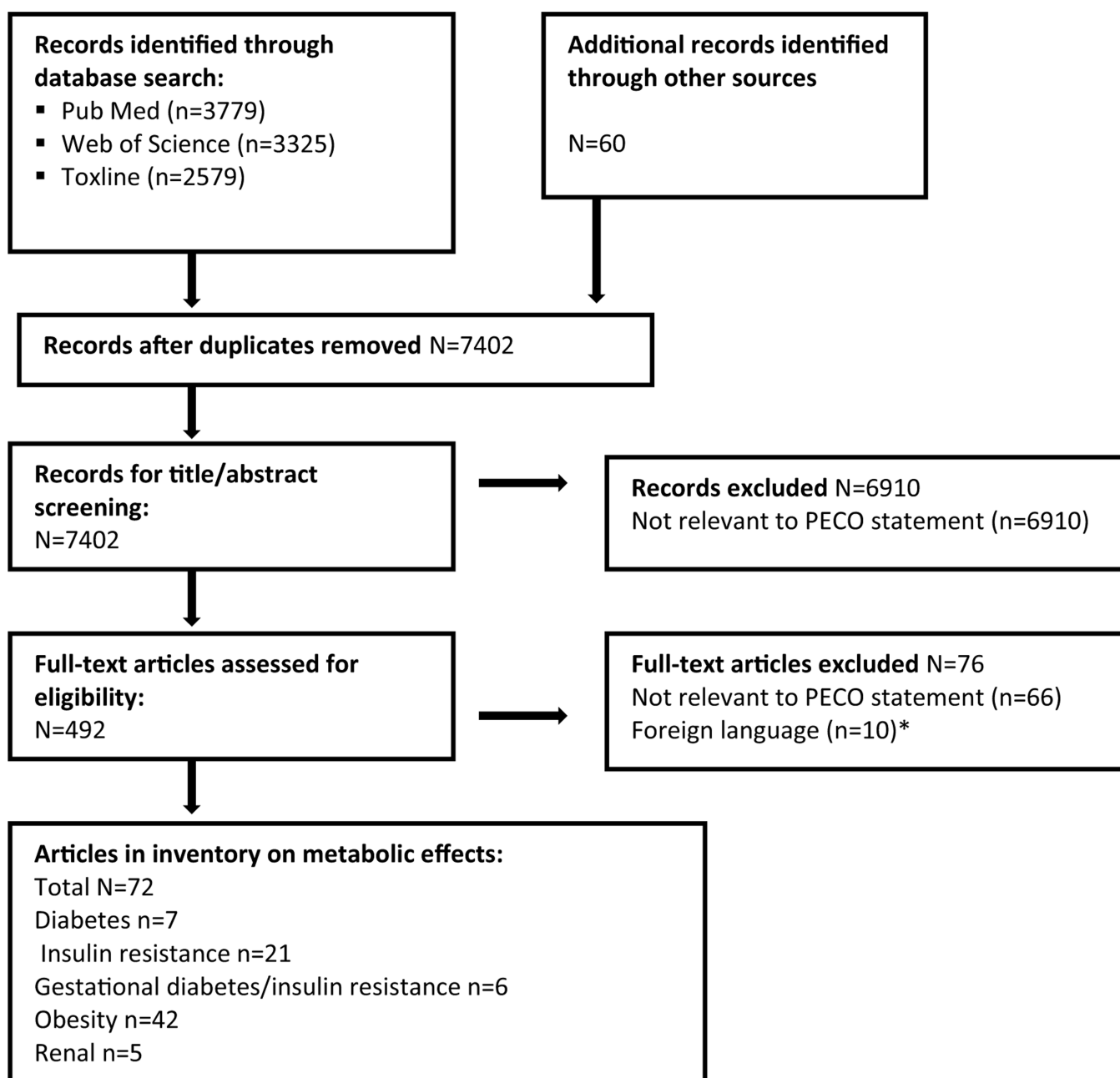
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**Fig. 1.**

Literature flow diagram for metabolic effects of phthalates.

\*Included one study on insulin resistance and one on obesity. Based on the abstracts, the former would be excluded due to exposure measurement in blood and the latter would be excluded due to temporality issues.

Number of articles in inventory does not account for multiple publications on the same study.

Table 1

Outcomes included in the review.

Outcome	Background and relevance to human health
Diabetes	<ul style="list-style-type: none"><li>Diabetes is a group of metabolic diseases characterized by hyperglycemia due to <math>\beta</math>-cell dysfunction, insulin resistance, or both. Diabetes can result in long-term complications in different organs, in particular, microvascular and macrovascular complications.</li></ul>
Insulin resistance	<ul style="list-style-type: none"><li>This review focuses on Type 2 (adult onset) diabetes.</li><li>Among study subjects without diabetes, fasting blood glucose, insulin, and a related measure based on the homeostatic model assessment of insulin resistance (HOMA-IR) are informative regarding future diabetes risk.</li></ul>
Gestational diabetes	<ul style="list-style-type: none"><li>Dysfunctions in insulin production and action in the peripheral tissues are the key pathways in diabetes etiology.</li><li>Gestational diabetes is another form of diabetes that occurs during pregnancy. A history of gestational diabetes is a risk factor for subsequent development of diabetes.</li></ul>
Obesity	<ul style="list-style-type: none"><li>Definitions of gestational diabetes and impaired glucose tolerance are based on measures of blood glucose. All three of these outcomes in pregnant women are reviewed together, separate from the general population.</li><li>Excessive body weight, or obesity, is associated with the leading causes of death worldwide, including diabetes, heart disease, stroke, and some types of cancer.</li></ul>
Renal effects	<ul style="list-style-type: none"><li>Body mass index (BMI) is a screening tool calculated from a person's weight and height that is moderately correlated with more direct measures of body fat (CDC 2016).</li><li>Kidney function can be assessed by measuring levels of urea, creatinine, and certain dissolved salts in blood and by analyzing protein levels in urine.</li><li>Albuminuria is a pathological condition wherein the protein albumin is abnormally present in the urine. Albuminuria is considered a significant risk factor for the development of renal disease.</li><li>Renal disease is a long-term complication of diabetes, obesity, and possibly, insulin resistance independent of those two conditions (Whaley-Connell and Sowers, 2017).</li><li>Impaired renal function could affect urinary concentration of phthalate metabolites.</li></ul>

Table 2

Epidemiology studies of diabetes.

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 Sun et al. (2014)	Case-control nested in two cohorts in U.S. (N=971 case-control pairs)	Single urine sample at least one year prior to diagnosis	Self-report of physician diagnosis (validated in cohort)	✓	✓	✓	✓	✓	✓	A/D	G	A	A	G	Medium

Excluded studies (6): exposure measured after development of outcome: James-Todd et al. (2012), Lind et al. (2012), Svensson et al. (2011), Castro-Correia et al. (2018), Dong et al. (2017), Piecha et al. (2016).

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

**Table 3**

Association between phthalate metabolites and type 2 diabetes in Sun et al. (2014).

Phthalate (metabolite)	NHS OR (95% CI)	NHSII OR (95% CI)	Pooled OR (95% CI) for Q4 vs. Q1
<b>DEHP (summed metabolites)</b>	DEHP Q2: 0.88 (0.52,1.50) Q3: 1.02 (0.61,1.71) Q4: 1.34 (0.77,2.30) $P_{\text{trend}}=0.1$	DEHP Q2: 1.80 (1.07,3.04) Q3: 1.62 (0.95,2.76) Q4: 1.91 (1.04,3.49) $P_{\text{trend}}=0.2$	MEOHP 1.42 (0.95,2.11)
<b>DBP+DIBP (MBP+MIBP)</b>	Q2: 1.26 (0.75,2.12) Q3: 1.01 (0.59,1.73) Q4: 0.91 (0.50,1.68) $P_{\text{trend}}=0.5$	Q2: 1.38 (0.81,2.35) Q3: 1.17 (0.66,2.10) Q4: 3.16 (1.68,5.95) $P_{\text{trend}}=0.0002$	n/a
<b>DBP (MBP)</b>	n/a	Q2: 1.53 (0.90,2.61) Q3: 1.18 (0.67,2.09) Q4: 3.16 (1.69,5.92) $P_{\text{trend}}=0.0003$	n/a
<b>DIBP (MIBP)</b>	n/a	Q2: 1.28 (0.76,2.13) Q3: 1.12 (0.62,2.02) Q4: 2.67 (1.44,4.95) $P_{\text{trend}}=0.001$	n/a
<b>BBP (MBzP)</b>	Q2: 0.91 (0.55,1.51) Q3: 0.85 (0.51,1.40) Q4: 0.82 (0.48,1.43) $P_{\text{trend}}=0.5$	Q2: 0.85 (0.50,1.44) Q3: 1.08 (0.62,1.86) Q4: 1.14 (0.65,2.01) $P_{\text{trend}}=0.4$	0.96 (0.65,1.43)
<b>DEP (MEP)</b>	Q2: 1.13 (0.69,1.84) Q3: 0.98 (0.60,1.61) Q4: 0.72 (0.43,1.20) $P_{\text{trend}}=0.09$	Q2: 1.00 (0.60,1.67) Q3: 0.46 (0.26,0.82) Q4: 0.91 (0.54,1.54) $P_{\text{trend}}=0.97$	0.80 (0.56,1.16)

Exposure levels presented in paper as medians of each quartile.

Results that support an association are shaded. Dark grey represents one or more of the following:  $p < 0.05$ , large effect size (e.g., OR 1.5), or exposure-response trend. Light grey represents other supportive results.

Epidemiology studies of insulin resistance (James-Todd et al., 2016a; Lin et al., 2016; Stahlhut et al., 2007).

Table 4

Reference	Study description	Includes metabolites of:										Study evaluation						
		Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP		Exposure	Outcome	Selection	Confounding	Analysis	Overall	confidence
Studies in Adults																		
Chen et al. (2017); Lin et al. (2016) <sup>a</sup>	Cross-sectional analysis of cohort in China of adults and adolescents, follow-up from mass urine screening of children (N=786)	Single urine sample collected in AM	Fasting blood glucose and insulin in serum. HOMA-IR calculated.	✓		✓		✓	✓		A/D	G	D	A	A	Medium		
Dales et al. (2018)	Cross-sectional in Canada (Canadian Health Measures Survey 2009–11) (N=2119 adults)	Single urine sample	Fasting blood glucose and insulin. HOMA-IR calculated	✓		✓		✓	✓		A/D	G	G	A	A	Medium		
Dirinck et al. (2015)	Cross-sectional in Belgium (N=123) of obese patients at weight clinic	24-hour urine collected day prior to visit	Fasting blood glucose and insulin collected in AM. HOMA-IR calculated.	✓		✓		✓	✓		A/D	A	D	A	A	Low		
Atina and Trasande (2015); Huang et al. (2014); James-Todd et al. (2016a); James-	Cross-sectional in U.S. (NHANES). Overlapping samples: 2001–08, 12–80 yrs 2001–10, 20–80 yrs	Single urine sample	Fasting blood glucose and insulin collected in AM. HOMA-	✓		✓		✓	✓		A/D	G	G	A	A	Medium		

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Included

Reference	Study description		Includes metabolites of:										Study evaluation			
	Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis	Overall	confidence
Todd et al. (2012); Stahlhut et al. (2007)	2001–08, Women 20–79 yrs 1999–2002, 18+ yrs (N=3,083 in Huang et al. (2014))		IR calculated.													
Hong et al. (2009)	Cross-sectional in Korea (N=1131 adults)	Single urine sample collected in AM	Fasting glucose and insulin in serum. HOMA-IR calculated.	✓	✓					A/D	A	D	A	D		Low
Hong et al. (2016)	Cross-sectional in Korea (N=296 women aged 30–49 yrs)	Single first AM urine sample	Fasting blood glucose and insulin collected in AM. HOMA-IR calculated	✓	✓					A/D	G	A	D	A		Medium
Kim and Hong (2014)	Cohort in Korea (N=560) of older adults (aged 60+)	Urine samples at up to 5 visits	Fasting glucose and insulin in serum. HOMA-IR calculated.	✓	✓					G	A	A	G	A		Medium
Kim et al. (2013)	enrolled through community center															
Studies in Adolescents																
Attina and Trasande (2015)	Cross-sectional in U.S. (NHANES). 2009–12, 12–19 yrs (N=356)	Single urine sample	Fasting blood glucose and insulin collected in AM. HOMA-	✓	✓	✓	✓	✓	✓	A/D	G	G	A	A		Medium

Reference	Study description		Includes metabolites of:								Study evaluation							Overall confidence
	Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis				
Trasande et al. (2013) <sup>a</sup>	Cross-sectional in U.S. (NHANES). 2003–08, 12–19 yrs (N=766)	Single urine sample	Fasting blood glucose and insulin collected in AM. HOMA-IR calculated.	✓	✓	✓	✓	✓	✓	A/D	G	G	A	A	Medium			
				Studies in Children														
Carlsson et al. (2018)	Cross-sectional in Thailand (N=107 healthy children)	Single first AM urine sample	Oral glucose tolerance test; insulin sensitivity index calculated	✓	✓	✓	✓	✓	✓	A/D	A	D	D	D	Low			
Kataria et al. (2017)	Cross-sectional pilot in U.S. (N=43 healthy children)	Single first AM urine sample	Fasting blood glucose and insulin collected in AM. HOMA-IR calculated	✓	✓					D	G	A	A	D	Low			
Saengkaew et al. (2017)	Cross-sectional of overweight/obese children and healthy controls (N=155)	Single AM urine sample	Fasting blood glucose and insulin collected in AM. HOMA-IR calculated			✓				A	G	D	D	D	Low			
Watkins et al. (2016)	Birth cohort in Mexico	Single maternal	Fasting glucose	✓	✓ <sup>b</sup>	✓ <sup>b</sup>				A/D	A	A	D	A	Medium			

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Reference	Study description		Includes metabolites of:							Study evaluation			
	Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding
	Subset of offspring (n=250/2,095) had follow-up at 8–14 yrs.	sample in 3 <sup>rd</sup> trimester; Single child sample at follow-up	and insulin in serum. HOMA-IR calculated.										

Excluded studies (3): exposure measurement based on tissue other than urine: Olsén et al. (2012). Approaches for confounding and analysis unclear, incomplete reporting of results: Smerieri et al. (2015), Milčević et al. (2017).

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

<sup>a</sup> Excluded estimates in adolescents.

<sup>b</sup> Study summed DBP and DIBP metabolites, and results discussed with DBP because it contributed a larger amount to the total.

Table 5

Association between DEHP metabolites and insulin resistance in adults and adolescents.

Reference; Study Confidence Rating; N	Median exposure	Exposure IQR	Effect estimate	Fasting glucose	Insulin	HOMA-IR
<b>DEHP in Adults</b>						
Huang et al. (2014); medium; 3,083	11.5 µmol/100 g creatinine (women)	6.5–23	Median change (95% CI)	Q2: 1.47 (0.3,2.63) Q3: 1.75 (0.66,2.84) Q4: 2.45 (1.29,3.60) $P_{\text{trend}}=0.0016^*$	Q2: 1.74 (1.04,2.45) Q3: 1.99 (1.31,2.66) Q4: 2.60 (1.82,3.38) $P_{\text{trend}}<0.0001^*$	Q2: 0.49 (0.31,0.66) Q3: 0.51 (0.34,0.69) Q4: 0.68 (0.47,0.88) $P_{\text{trend}}<0.0001^*$
Dales et al. (2016); medium; 2,119	47 ng/mL		$\beta$ (95% CI) for IQR increase	0.04 (0.00,0.08) <sup>*</sup>	0.63 (0.21,1.05) <sup>*</sup>	0.15 (0.04,0.26) <sup>*</sup>
<b>MEOHP in Adults</b>						
Dirinck et al. (2015); low; 123	6.2 µg/g creatinine	0.8–42 (range)	$\beta$ (95% CI)	3.88 (−6.19,13.95)	26.62 (0.69,52.5) <sup>*</sup>	0.31 (−0.72,0.69)
Hong et al. (2016); medium; 296	6.5 µg/g creatinine	3.9–10	$\beta$ (95% CI)	0.12 (−1.11,1.36)	0.14 (−0.08,0.36)	0.12 (−0.08,0.33)
Chen et al. (2017); medium; 552	17 µg/g creatinine	16	$\beta$ (95% CI)	−0.001 (−0.01,0.01)	0.003 (−0.07,0.07)	0.001 (−0.07,0.07)
Kim et al. (2013) medium; 560	19 ng/mL	9.5–33	$\beta$ (95% CI)	0.11 (0.01,0.22) <sup>†</sup>	0.70 (0.01,1.40) <sup>†</sup>	0.26 (0.01,0.51) <sup>†</sup>
<b>MEOHP in Adolescents</b>						
Chen et al. (2017); medium; 234	17 µg/g creatinine	16	$\beta$ (95% CI)	0.001 (−0.01,0.01)	0.04 (−0.05,0.12)	0.04 (−0.05,0.13)
Attina and Trasande (2015); medium; 356	0.14 µM		$\beta$ (95% CI)	NR	NR	0.06 (−0.001,0.12)
Trasande et al. (2013); medium; 766	NR		$\beta$ (95% CI)	NR	NR	0.27 (0.14,0.40) <sup>*</sup>

Results that support an association are shaded based on effect size and precision. Dark grey represents one or more of the following:  $p < 0.05$ , large effect size (e.g., OR 1.5,  $\beta$  0.5), or exposure-response trend. Light grey represents other supportive results. Strength of the evidence (i.e., contribution to the synthesis conclusions) from an individual study is influenced by other factors, such as study confidence.

<sup>\*</sup>  $p < 0.05$ .

<sup>†</sup> Estimates for total population, including those with history of diabetes. Association for the strata without history of diabetes was not reported.

Hong et al. (2009) reported that no significant association was observed but did not provide quantitative estimates.

**Table 6**  
Association between DBP metabolites and insulin resistance in adults and adolescents.

Reference	Median MBP	Exposure IQR	Effect estimate	Fasting glucose	Insulin	HOMA-IR
Adults						
Huang et al. (2014); medium; 3,083	22 µg/g creatinine	13–36	Median change (95% CI)	Q2: 0.95 (−0.22,2.13) Q3: 1.70 (0.51,2.89) Q4: 1.91 (0.51,3.31)	Q2: 1.15 (0.52,1.78) Q3: 1.41 (0.72,2.09) Q4: 1.11 (0.31,1.92)	Q2: 0.28 (0.11,0.44) Q3: 0.28 (0.11,0.46) Q4: 0.34 (0.15,0.54)
				$P_{\text{trend}}=0.019^*$	$P_{\text{trend}}<0.09$	$P_{\text{trend}}<0.006^*$
Hong et al. (2016); medium; 296	30 µg/g creatinine	21–42	$\beta$ (95% CI)	−0.37 (−1.38,0.65)	0.06 (−0.13,0.24)	0.04 (−0.13,0.21)
<b>Dales et al. (2016)</b> ; medium, 2,119	31 ng/mL		$\beta$ (95% CI) for IQR increase	0.00 (−0.06,0.06)	0.47 (−0.02,0.96)	0.08 (−0.09,0.24)
Chen et al. (2017); medium; 552	38 µg/g creatinine	41	$\beta$ (95% CI)	0.01 (−0.002,0.01)	0.01 (−0.06,0.08)	0.02 (−0.05,0.09)
Dirinck et al. (2015); low; 123	38 µg/g creatinine	3.9–370 (range)	$\beta$ (95% CI)	7.27 (−1.29,15.83)	22.52 (3.13,41.90) <sup>*</sup>	0.29 (−0.05,0.63)
Kim et al. (2013); medium; 560	57 ng/mL	29–158	$\beta$ (95% CI)	0.06 (−0.04,0.17) <sup>‡</sup>	0.38 (−0.30,1.07) <sup>‡</sup>	0.16 (−0.09,0.40) <sup>‡</sup>
Adolescents						
Chen et al. (2017); medium; 234	38 µg/g creatinine	41	$\beta$ (95% CI)	0.01 (−0.001,0.02)	0.002 (−0.08,0.08)	0.01 (−0.07,0.10)
Atina and Trasande (2015); medium; 356	NR	NR	$\beta$ (95% CI)	NR	NR	0.05 (−0.02,0.12)
Trasande et al. (2013); medium; 766	NR	NR	$\beta$ (95% CI)	NR	NR	0.13 (0.01,0.26) <sup>*</sup>

Results that support an association are shaded based on effect size and precision. Dark grey represents one or more of the following:  $p < 0.05$ , large effect size (e.g., OR 1.5,  $\beta$  0.5), or exposure-response trend. Light grey represents other supportive results. Strength of the evidence (i.e., contribution to the synthesis conclusions) from an individual study is influenced by other factors, such as study confidence.

<sup>\*</sup>  $p < 0.05$ .

<sup>‡</sup> Estimates for total population, including those with history of diabetes. Association for the strata without history of diabetes was not reported.

Hong et al. (2009) reported that no significant association was observed, but did not provide quantitative estimates.

**Table 7**  
Association between DIBP metabolites and insulin resistance in adults and adolescents.

Reference	Median MIBP	Exposure IQR	Effect estimate	Fasting glucose	Insulin	HOMA-IR
Adults						
Huang et al. (2014); medium; 3,083	4.9 µg/g creatinine (women)	2.6–8.9	Median change (95% CI)	Q2: 1.87 (0.83,2.92) Q3: 2.77 (1.75,3.80) Q4: 3.69 (2.60,4.78) P <sub>trend</sub> <0.0001	Q2: 1.45 (0.85,2.04) Q3: 1.23 (0.57,1.89) Q4: 1.73 (0.92,2.54) P <sub>trend</sub> =0.0003	Q2: 0.38 (0.23,0.52) Q3: 0.35 (0.19,0.51) Q4: 0.53 (0.33,0.72) P <sub>trend</sub> =0.0002 *
Dales et al. (2016); medium, 2,119	13 ng/mL		β (95% CI) for IQR increase	0.00 (−0.02,0.03)	0.00 (−0.19,0.19)	0.00 (−0.05,0.05)
Dirinck et al. (2015); low; 123	57 µg/g creatinine	7.5–55 (range)	β (95% CI)	5.44 (−3.57,14.5)	7.69 (−15.9,31.3)	0.15 (−0.18,0.47)
Adolescents						
Attina and Trasande (2015); medium; 356	NR		β (95% CI)	NR	NR	0.03 (−0.05,0.11)
Trasande et al. (2013); medium; 766	NR		β (95% CI)	NR	NR	0.15 (0.04, 0.26) *

Results that support an association are shaded based on effect size and precision. Dark grey 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. Light grey represents other supportive results. Strength of the evidence (i.e., contribution to the synthesis conclusions) from an individual study is influenced by other factors, such as study confidence.

\*  $p < 0.05$ .

<sup>†</sup> Estimates for total population, including those with history of diabetes. Association for the strata without history of diabetes was not reported.

Table 8

Association between BBP metabolites and insulin resistance in adults and adolescents.

Reference	Median MBzP	Exposure IQR	Effect estimate	Fasting glucose	Insulin	HOMA-IR
Adults						
Chen et al. (2017); medium; 552	1.9 µg/g creatinine	2.4	β (95% CI)	−0.002 (−0.01,0.004)	−0.05 (−0.12,0.01)	−0.06 (−0.12,0.01)
<b>Dales et al. (2016)</b> ; medium; 2,119	8.4 ng/mL		β (95% CI) for IQR increase	0.00 (−0.02,0.02)	0.03 (−0.20,0.26)	0.00 (−0.06,0.06)
Huang et al. (2014); medium; 3,083	13 µg/g creatinine (women)	7.1–24	Median change (95% CI)	Q2: −0.30 (−1.48,0.87) Q3: −0.06 (−1.25,1.13) Q4: −0.24 (−1.49,1.02)	Q2: 0.77 (0.16,1.39) Q3: 1.09 (0.39,1.79) Q4: 1.44 (0.50,2.38)	Q2: 0.21 (0.06,0.37) Q3: 0.26 (0.09,0.44) Q4: 0.37 (0.15,0.59)
				P <sub>trend</sub> =0.7	P <sub>trend</sub> =0.007 *	P <sub>trend</sub> <0.003 *
Dirinck et al. (2015); low; 123	8.7 µg/g creatinine	0.7–90 (range)	β (95% CI)	8.74 (1.42,16.06) *	14.90 (4.38,34.18)	0.15 (−0.16,0.46)
Adolescents						
Chen et al. (2017); medium; 234	1.9 µg/g creatinine	2.4	β (95% CI)	−0.002 (−0.01,0.01)	0.03 (−0.06,0.13)	0.03 (−0.07,0.13)
Attina and Trasande (2015); medium; 356	NR		β (95% CI)	NR	NR	0.03 (−0.03,0.09)
Trasande et al. (2013); medium; 766	NR		β (95% CI)	NR	NR	0.02 (−0.08,0.13)

Results that support an association are shaded based on effect size and precision. Dark grey 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. Light grey represents other supportive results. Strength of the evidence (i.e., contribution to the synthesis conclusions) from an individual study is influenced by other factors, such as study confidence.

\*  $p < 0.05$ .

<sup>†</sup> Estimates for total population, including those with history of diabetes. Association for the strata without history of diabetes was not reported.

**Table 9**

Association between DEP metabolites and insulin resistance in adults and adolescents.

Reference	Median MEP	Exposure IQR	Effect estimate	Fasting glucose	Insulin	HOMA-IR
<b>Adults</b>						
Dales et al. (2016); medium, 2,119	8.4 ng/mL		$\beta$ (95% CI) for IQR increase	0.00 (−0.02,0.03)	0.00 (−0.27,0.27)	−0.01 (−0.08,0.06)
Chen et al. (2017); medium; 552	32 $\mu\text{g/g}$ creatinine	63	$\beta$ (95% CI)	0.00 (−0.01,0.01)	−0.04 (−0.10,0.01)	−0.04 (−0.10,0.01)
Huang et al. (2014); medium; 3,083	182 $\mu\text{g/g}$ creatinine (women)	89–426	Median change (95% CI)	Q2: 1.30 (0.15,2.46) Q3: 0.38 (−0.75,1.51) Q4: 0.49 (−0.80,1.77)	Q2: 0.25 (−0.50,0.99) Q3: 0.34 (−0.35,1.02) Q4: 0.60 (−0.13,1.34)	Q2: 0.11 (−0.06,0.27) Q3: 0.10 (−0.07,0.28) Q4: 0.20 (0.03,0.38)
				$P_{\text{trend}}=0.8$	$P_{\text{trend}}=0.15$	$P_{\text{trend}}<0.006^*$
<b>Adolescents</b>						
Dirinck et al. (2015); low; 123	81 $\mu\text{g/g}$ creatinine	3.4–6865 (range)	$\beta$ (95% CI)	1.31 (−3.23,5.85)	9.81 (−1.88,21.5)	0.15 (−0.022,0.31)
Chen et al. (2017); medium; 234	32 $\mu\text{g/g}$ creatinine	63	$\beta$ (95% CI)	0.001 (−0.01,0.01)	−0.02 (−0.08,0.05)	−0.02 (−0.08,0.05)
Attina and Trasande (2015); medium; 356	NR		$\beta$ (95% CI)	NR	NR	0.02 (−0.05,0.05)
Trasande et al. (2013); medium; 766	NR		$\beta$ (95% CI)	NR	NR	−0.07 (−0.16,0.03)

Results that support an association are shaded based on effect size and precision. Dark grey represents one or more of the following:  $p < 0.05$ , large effect size (e.g., OR 1.5,  $\beta$  0.5), or exposure-response trend. Light grey represents other supportive results. Strength of the evidence (i.e., contribution to the synthesis conclusions) from an individual study is influenced by other factors, such as study confidence.

\*  $p < 0.05$ .

$\overline{F}$  Estimates for total population, including those with history of diabetes. Association for the strata without history of diabetes was not reported.

Table 10

Epidemiology studies of gestational diabetes and blood glucose in pregnancy.

Reference	Study description		Includes metabolites of:								Study evaluation					Overall confidence
	Population	Exposure	Outcome	DEHP	DINP	DBP	DIBP	BBP	DEP	Exposure	Outcome	Selection	Confounding	Analysis		
Studies in Adults																
James-Todd et al. (2016b)	Sample of women from pregnancy cohort in U.S. (N=352)	Urine samples collected at up to 4 prenatal visits	Impaired glucose tolerance and blood glucose during oral glucose tolerance test	✓	✓	✓	✓	✓	✓	G/A	G	A	A	A	Medium	
James-Todd et al. (2018)	Cohort of women seeking infertility evaluation/treatment in U.S. (N=245)	Urine samples collected in each trimester	Impaired glucose tolerance and blood glucose during oral glucose tolerance test	✓	✓	✓	✓	✓	✓	G/A	G	G	G	G	High	
Robledo et al. (2015)	Pilot cohort of pregnant women in U.S. (N=72) enrolled at first prenatal visit	Single urine sample	Blood glucose during oral glucose tolerance test.	✓	✓	✓	✓	✓	✓	A/D	D	A	A	A	Low	
Shapiro et al. (2015)	Cohort of pregnant women in U.S. (N=1,885) enrolled in first trimester	Single urine sample	Gestational diabetes and impaired glucose tolerance diagnosed from glucose challenge test	✓	✓	✓	✓	✓	✓	A/D	A	A	A	A	Medium	

Included

Excluded studies (2): exposure measurement based on tissue other than urine and high percent non-detects for secondary metabolites of DEHP; Fisher et al. (2018); unable to obtain full text; Zhang et al. (2017).

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

<sup>a</sup> Included estimates in adolescents.



Table 11

Association between DEHP and blood glucose in pregnant women.

Reference	Median Exposure	Exposure IQR	Blood glucose 1 <sup>st</sup> trimester Mean (95% CI)	Blood glucose 2 <sup>nd</sup> trimester Mean (95% CI)	Impaired glucose tolerance * OR (95%)
James-Todd et al., (2016b) medium; 352	0.4 nmol/l (GM)	0.2–0.8	Q1: 110 (100,120) Q2: 115 (105, 127) Q3: 108 (98,118) Q4: 114 (104, 126)	Q1: 117 (106,129) Q2: 110 (100,121) Q3: 109 (99,120) Q4: 110 (100,121) p-trend: 0.16	Q2: 0.46 (0.15,1.40) Q3: 0.74 (0.27,2.04) Q4: 0.25 (0.08,0.85) p-trend: 0.06
James-Todd et al. (2018) high; 245	0.2 nmol/l	0.1–0.4	Q1: 116 (109,123) Q2: 114 (107,121) Q3: 114 (107,121) Q4: 113 (107,120)	Q1: 111 (105,118) Q2: 111 (105,118) Q3: 115 (109,122) Q4: 116 (109, 123)	no association
Shapiro et al. (2015) medium; 1,885	7.4 (MEOHP) 11 (MEHHP) 2.6 (MEHP) ng/mL	NR	NR	NR	Q2: 1.0 (0.5,2.0) Q3: 0.6 (0.3,1.5) Q4: 0.9 (0.4,2.3)
Robledo et al. (2015) low; 72	66 ng/mL	37–101	NR	$\beta$ (95% CI) T2: 3.82 (–10.22,17.86) T3: –9.97 (–27.11,7.17)	NR

Results that support an association are shaded based on effect size and precision.

\* Shapiro includes impaired glucose tolerance and gestational diabetes.

p-Values &gt;0.20 are not presented. NR= not reported.

Table 12

Association between DBP and DIBP and blood glucose in pregnant women.

Reference	Median Exposure (ng/mL)	Exposure IQR	Blood glucose 1 <sup>st</sup> trimester Mean (95% CI)	Blood glucose 2 <sup>nd</sup> trimester Mean (95% CI)	Impaired glucose tolerance * OR (95%)
James-Todd et al., (2016b) medium; 352	18 (GM)	11–27	Q1: 115 (104,126) Q2: 113 (103,124) Q3: 114 (103,125) Q4: 109 (99,119) p-trend: 0.13	Q1: 111 (100,123) Q2: 113 (103,125) Q3: 114 (104,125) Q4: 108 (98,119)	Q2: 0.95 (0.31,2.91) Q3: 1.26 (0.43,3.68) Q4: 1.14 (0.37,3.51)
<b>DBP</b>					
James-Todd et al. (2018) high; 245	12	6.8–21	Q1: 116 (109,123) Q2: 112 (105,118) Q3: 116 (109, 123) Q4: 113 (107,120)	Q1: 112 (106,119) Q2: 113 (106,120) Q3: 114 (107,121) Q4: 115 (109,122)	no association
Shapiro et al. (2015) medium; 1,885	13	NR	NR	NR	Q2: 1.8 (0.9,3.6) Q3: 1.3 (0.6,3.0) Q4: 0.8 (0.3,2.2) p-trend: 0.51
Robledo et al. (2015) low; 72	29	16–57	NR	$\beta$ (95% CI) T2: 0.11 (–14.71,14.93) T3: –15.61 (–32.99,1.76)	NR
<b>DIBP</b>					
James-Todd et al., (2016b) medium; 352	7.3 (GM)	4.5–12	Q1: 114 (103,125) Q2: 111 (101,123) Q3: 114 (103,125) Q4: 110 (100,121) p-trend: 0.17	Q1: 111 (100,122) Q2: 109 (99,120) Q3: 110 (100,121) Q4: 114 (104,126)	Q2: 0.47 (0.14,1.58) Q3: 1.16 (0.38,3.54) Q4: 1.79 (0.62,5.16) p-trend: 0.18
James-Todd et al. (2018) high; 245	6.2	3.3–10	Q1: 118 (111,125) Q2: 114 (107,121) Q3: 114 (107,121) Q4: 111 (104,117)	Q1: 119 (113,126) Q2: 115 (109,122) Q3: 115 (109, 122) Q4: 105 (99,111)	0.37 (0.12,1.16)

Reference	Median Exposure (ng/mL)	Exposure IQR	Blood glucose 1 <sup>st</sup> trimester Mean (95% CI)	Blood glucose 2 <sup>nd</sup> trimester Mean (95% CI)	Impaired glucose tolerance * OR (95%)
Robledo et al. (2015) low; 72	11	6.7–18	NR	<p>p-trend: 0.003</p> <p><math>\beta</math> (95% CI)</p> <p>T2: -2.01 (-16.18,12.17)</p> <p>T3: -18.30 (-35.41,-1.19)</p>	NR

Results that support an association are shaded based on effect size and precision.

\* Shapiro includes impaired glucose tolerance and gestational diabetes.

*p*-Values >0.20 are not presented. NR= not reported.

Table 13

Association between BBP and DEP and blood glucose in pregnant women.

Reference	Median Exposure (ng/mL or as specified)	Exposure IQR	Blood glucose 1 <sup>st</sup> trimester Mean (95% CI)	Blood glucose 2 <sup>nd</sup> trimester Mean (95% CI)	Impaired glucose tolerance* OR (95%)
James-Todd et al. (2016b) medium; 352	7.4 (GM)	3.3–15	Q1: 108 (98,119) Q2: 118 (108,130) Q3: 112 (102, 122) Q4: 111 (102,122)	Q1: 106 (96,118) Q2: 113 (102,126) Q3: 114 (103,125) Q4: 110 (101,121)	Q2: 1.17 (0.40,3.48) Q3: 1.16 (0.39,3.49) Q4: 1.28 (0.40,4.07)
James-Todd et al. (2018) high; 245	2.8	1.4–5.4	Q1: 113 (107,120) Q2: 117 (110,124) Q3: 110 (103,116) Q4: 117 (110,124)	Q1: 111 (105,118) Q2: 117 (110,124) Q3: 110 (104,117) Q4: 116 (109,123)	no association
Shapiro et al. (2015) medium; 1,885	5.8	NR	NR	NR	Q2: 1.3 (0.6,2.8) Q3: 2.0 (0.9, 4.4) Q4: 2.0 (0.9,4.8) p-trend: 0.07
Robledo et al. (2015) low; 72	16	8.5–37	NR	$\beta$ (95% CI) T2: -0.82 (-14.37,12.73) T3: -17.26 (-34.12,-0.40)	NR
James-Todd et al., (2016b) medium; 352	133 (GM)	49–325	Q1: 113 (103,125) Q2: 114 (103,125) Q3: 115 (105,126) Q4: 107 (98,118)	Q1: 109 (100,120) Q2: 112 (102,124) Q3: 110 (99,121) Q4: 116 (105,128) p-trend: 0.19	Q2: 2.14 (0.57,8.10) Q3: 2.53 (0.71,8.97) Q4: 7.18 (1.97,26.15) p-trend: <0.01
James-Todd et al. (2018) high; 245	48	22–144	Q1: 114 (108,121) Q2: 115 (108,122) Q3: 109 (103,116) Q4: 118 (111,125)	Q1: 109 (103,116) Q2: 113 (107,120) Q3: 111 (105,117) Q4: 121 (114,128) p-trend: 0.02	2.48 (0.86,7.20)

Reference	Median Exposure (ng/mL or as specified)	Exposure IQR	Blood glucose 1 <sup>st</sup> trimester Mean (95% CI)	Blood glucose 2 <sup>nd</sup> trimester Mean (95% CI)	Impaired glucose tolerance* OR (95%)
Shapiro et al. (2015) medium; 1,885	39	NR	NR	NR	Q2: 1.0 (0.5,2.0) Q3: 0.8 (0.4,1.7) Q4: 0.7 (0.3,1.5) p-trend: 0.29
Robledo et al. (2015) low; 72	206	92–525	NR	$\beta$ (95% CI) T2: 4.45 (–9.30,18.19) T3: 0.18 (–14.57,14.94)	NR

Results that support an association are shaded based on effect size and precision.

\* Shapiro includes impaired glucose tolerance and gestational diabetes.

p-Values >0.20 are not presented. NR= not reported.

Table 14

Summary of evidence for diabetes risk in adults.

Phthalate	Outcome	Studies	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Evidence judgment
DEHP	Diabetes	Medium confidence Sun et al. (2014) (nested CC in two C)	<ul style="list-style-type: none"> <li>Study well conducted</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> <li>Imprecision</li> </ul>	Positive association between DEHP exposure and type 2 diabetes diagnosis (not statistically significant, Table 3).	⊕⊕⊕ MODERATE for diabetes risk
	Insulin resistance in adults	Medium confidence Chen et al. (2017) (CS) Dales et al. (2018) (CS) Hong et al. (2016) (CS) Huang et al. (2014) (CS) Kim et al. (2013) (C) Low confidence Dirinck et al. (2015) (CS) Hong et al. (2009) (CS)	<p>Among medium confidence studies:</p> <ul style="list-style-type: none"> <li>Exposure-response gradient observed in one study</li> <li>Generally consistent results across populations</li> <li>Minimal concerns for bias</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> </ul>	Positive association between DEHP exposure and glucose, insulin and/or HOMA-IR in 5 studies (Dales et al., 2018; Dirinck et al., 2015; Huang et al., 2014; Kim et al., 2013; Hong et al., 2016), with statistical significance in four (Table 5). Exposure-response gradients were reported in Huang et al. (2014) for all endpoints (not evaluated in other studies)	Supported by coherence across outcomes and plausible mechanism from animal and in vitro studies
DINP	Insulin resistance in adolescents	Medium confidence Atina and Trasande (2015) (CS)	<ul style="list-style-type: none"> <li>Minimal concerns for bias</li> <li>Exposure-response gradient</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> </ul>	Positive association between DINP exposure and HOMA-IR, with statistical significance in the third tertile.	⊕⊕⊕ SLIGHT
DBP	Diabetes	Medium confidence Sun et al. (2014) (nested CC in two C)	<ul style="list-style-type: none"> <li>Strong association</li> <li>Study well conducted</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> </ul>	Strong positive (OR=3.2 for Q4) statistically significant association between DBP exposure and type 2 diabetes diagnosis (Table 3).	⊕⊕⊕ MODERATE
	Insulin resistance in adults	Medium confidence Chen et al. (2017) (CS) Dales et al. (2018) (CS) Hong et al. (2016) (CS) Huang et al. (2014) (CS) Kim et al. (2013) (C) Low confidence Dirinck et al. (2015) (CS) Hong et al. (2009) (CS)	<p>Among medium confidence studies:</p> <ul style="list-style-type: none"> <li>Exposure-response gradient observed in one study</li> <li>Minimal concerns for bias</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> </ul>	Positive association between DBP exposure and at least one measure of insulin resistance (i.e., glucose, insulin and/or HOMA-IR) in 4 studies (Huang et al., 2014; Dirinck et al., 2015; Dales et al., 2018; Kim et al., 2013), with statistical significance in 2 (Table 6). An exposure-response gradient was reported in Huang et al. (2014) for glucose (not evaluated in other studies).	Supported by coherence across outcomes and plausible mechanism from animal and in vitro studies
	Diabetes	Medium confidence Sun et al. (2014) (nested CC in two C)	<ul style="list-style-type: none"> <li>Strong association</li> <li>Study well conducted</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> </ul>	Strong positive (OR=2.7 for Q4) statistically significant association between DIBP exposure and type 2 diabetes diagnosis (Table 3).	⊕⊕⊕ MODERATE
DIBP	Insulin resistance in adults	Medium confidence Dales et al. (2018) (CS) Huang et al. (2014) (CS) Low confidence Dirinck et al. (2015) (CS)	<ul style="list-style-type: none"> <li>Exposure-response gradient observed in one study</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Few studies</li> </ul>	Positive association between DIBP exposure and glucose, insulin, and/or HOMA-IR in 2 studies (Huang et al., 2014) (Dirinck et al., 2015) (Table 7). Huang et al. (2014) reported statistical significance for all endpoints and an exposure-response gradient for glucose (not evaluated in other study)	Supported by coherence across outcomes and plausible mechanism from animal and in vitro studies

Phthalate	Outcome	Studies	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Evidence judgment
BBP	Diabetes	Medium confidence Sun et al. (2014) (nested CC in two C)	<ul style="list-style-type: none"> <li>Study well conducted</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> </ul>	No association reported between type 2 diabetes risk and BBP exposure.	⊕⊕⊕ SLIGHT
	Insulin resistance in adults	Medium confidence Chen et al. (2017) (CS) Dales et al. (2018) (CS) Huang et al. (2014) (CS) Low confidence Dirinck et al. (2015) (CS)	<ul style="list-style-type: none"> <li>Exposure-response gradient observed in one study</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Few studies</li> <li>Inconsistency among medium confidence studies</li> </ul>	Positive association between BBP exposure and glucose, insulin, and/or HOMA-IR in 2 studies (Dirinck et al., 2015; Huang et al., 2014) (Table 8). Exposure-response gradients were observed for insulin and HOMA-IR in Huang et al. (2014) (not evaluated in other study).	⊕⊕⊕ SLIGHT
DEP	Diabetes	Medium confidence Sun et al. (2014) (nested CC in two C)	<ul style="list-style-type: none"> <li>Study well conducted</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Single study</li> </ul>	No association reported between type 2 diabetes risk and DEP exposure.	⊕⊕⊕ SLIGHT
	Insulin resistance in adults	Medium confidence Chen et al. (2017) (CS) Dales et al. (2018) (CS) Huang et al. (2014) (CS) Low confidence Dirinck et al. (2015) (CS)	<ul style="list-style-type: none"> <li>Exposure-response gradient observed in one study</li> <li>Consistent results across populations</li> </ul>	<ul style="list-style-type: none"> <li>Potential for residual confounding by diet</li> <li>Few studies</li> </ul>	Positive association between DEP exposure and glucose, insulin and/or HOMA-IR in 2 studies (Huang et al., 2014) (Dirinck et al., 2015) (Table 9). Exposure-response gradients were observed for insulin and HOMA-IR in (Huang et al., 2014) (not evaluated in other study).	⊕⊕⊕ SLIGHT

C=cohort; CC=case-control; CS=cross-sectional.