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Phthalate exposure and childrens neurodevelopment: A systematic review

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ABSTRACT

Background: Emerging evidence from observational studies suggests that prenatal exposure to phthalates affects neurodevelopment in children.
Objective: To conduct a systematic review of the existing literature on the association between urinary phthalate concentrations and children's neurodevelopment.
Methods: We searched electronic bibliographic databases (MEDLINE, PubMed, EMBASE, PsycINFO, CINAHL, Global Health, CAB abstracts, and ERIC) (1910 to February 21st, 2014); reference lists of included articles, and conference abstracts (American Psychiatric Association, American Academy of Neurology, and Pediatric Academic Societies). Two independent reviewers screened abstracts and extracted data. We included original studies reporting on the association between prenatal or childhood urinary phthalate metabolites, and cognitive and behavioral outcomes (e.g., IQ scores, BASC-2 scores or equivalent) in children 0–12 years of age.
Results: Of 2804 abstracts screened, 11 original articles met our criteria for inclusion.
Conclusions: A systematic review of the literature supports the contention that prenatal exposure phthalates is associated with adverse cognitive and behavioral outcomes in children, including lower IQ, and problems with attention, hyperactivity, and poorer social communication. Further research characterizing the associations between specific phthalate metabolites and children's neurodevelopmental outcomes is needed to support the development of mitigation strategies and enhance the development of appropriate health policy.

1. Introduction

Phthalates are endocrine disrupting chemicals (EDC) derived from phathalic acid. They were first introduced in the 1920s and are used in a variety of products including personal care products, plastics, flooring and medical tubing. Every year, approximately 4.99 million metric tons of phthalates are produced worldwide ("Phthalates and their alternatives: Health and environmental concerns," 2011). Phthalates are lipid soluble, have relatively short (less than 24 h) half-lives, and do not accumulate appreciably in the body (Koch et al., 2007, 2006; Wittassek and Angerer, 2008). Phthalate metabolite levels can be measured in the blood, breast milk, and meconium (Janjua et al., 2007; Main et al., 2006; Zhang et al., 2009). However, urine samples are the most common, reliable, and non-invasive means of measuring phthalates in human populations (Braun et al., 2012; Hauser et al., 2004; Needham et al., 2005) and exposure is typically measured by urinary metabolite concentrations. Table 1 provides a summary of common phthalates and their corresponding urinary metabolites.

Molecular weight and chemical properties determine the types of products in which phthalates are used. Low molecular weight (LMW) phthalates (<50 Da), such as dimethyl phthalate (DMP), diethyl phthalate (DEP), and dibutyl phthalate (DBP), are used in cosmetic products and lotions, and as aerosol delivery agents. As a result, ubiquitous daily exposure in adults and children is expected (CDC, 2011). Usage of personal care products by adults and children has been associated with elevated urinary phthalate metabolite concentrations. For example, Sathyanarayana (2008) found higher levels of several phthalate metabolites, including monoethyl phthalate (MEP) monomethyl phthalate (MMP), and monoisobutyl phthalate (MiBP), in infants whose mother reported exposure to baby lotion, powder or shampoo in the last 24 h. Higher phthalate metabolite concentrations were positively associated with the number of products used. Phthalates are also used in coatings of pharmaceutical tablets and both a case report and a

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Table 1
Common phthalates and their urinary metabolites.

	Phthalate name	Abbreviation	Urinary metabolite	Abbreviation
Low molecular weight	Dimethyl phthalate	DMP	Mono-methyl phthalate	MMP
	Diethyl phthalate	DEP	Mono-ethyl phthalate	MEP
	Dibutyl phthalates	DBP	Mono-n-butyl phthalate Mono-isobutyl phthalate	MnBP[a] MiBP[a]
High molecular weight	Benzylbutyl phthalate	BzBP	Mono-benzyl phthalate	MBzP
	Di-2-ethylhexyl phthalate	DEHP[b]	Mono-2-ethylhexyl phthalate	MEHP
			Mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
			Mono-(2-ethyl-5-oxohexyl) phthalate	MEOHP
			Mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP
	Di-n-octyl phthalate	DOP	Mono-(3-carboxypropyl) phthalate Mono-n-octyl phthalate	MCPP MOP
	Di-isononyl phthalate	DiNP	Mono-isononyl phthalate	MiNP
	Di-isodecyl phthalate	DiDP	Mono-(carboxynonyl) phthalate	MCNP

[a] Sum of MnBP and MiBP are referred as MBP.
[b] Also known as DnOP.

cross sectional study showed high levels of urinary DEP and DBP metabolite among adults using medications such as theophylline, mesalamine, omeprazole, and didanosine (Hauser et al., 2004; Hernandez-Diaz et al., 2009). The use of phthalate coatings in pharmaceutical tablets is of special concern, particularly in vulnerable populations such as pregnant women and children. Their use in medical devices and tubing is also troubling as phthalate metabolites can "easily leach out of tubing when heated (as with warm saline/blood)" (Sathyanarayana, 2008), putting hospitalized pregnant women, infants and children at high risk of exposure (Koch et al., 2005).

High molecular weight phthalates (>50 Da), such as di(2-ethylhexyl) phthalate (DEHP), butylbenzyl phthalate (BBzP), di(n-octyl) phthalate (DOP), diisononyl phthalate (DiNP), and diisodecyl phthalate (DiDP), are mainly used as plasticizers and adhesives. While increasing flexibility, transparency, and durability, HMW phthalates can leach from products over time (Bornehag et al., 2005; Carlstedt et al., 2013). Thus, they may leach into food products from containers in which food is stored. A randomized control trial suggested that exposure to phthalates can be reduced by eliminating the use of plastic materials in food preparation and storage (Rudel et al., 2011).

Concerns have been raised over the impact of phthalates on the development of offspring. In vitro studies have revealed that phthalates have estrogenic activity (Jobling et al., 1995; Sumpter, 1995), can pass through the placenta, and enter breast milk (Janjua et al., 2007; Main et al., 2006; Zhang et al., 2009). A biomonitoring study that examined phthalate metabolite concentrations in the Canadian population revealed that both LMW and HMW phthalate metabolites (i.e., MEP, MnBP, MBzP, MEHP, MEHHP and MEOHP) were detected in more than 99% of the samples, while MCPP (metabolite derivative of DOP, a HMW phthalate) was found in in 90% of the samples (Saravanabhavan et al., 2013). Data from the National Health and Nutrition Examination Survey (NHANES) in the USA indicated that children 6–11 years age had higher concentrations of both LMW and HMW phthalate metabolites (i.e., MBP, MBzP and MEHP) relative to adults (Silva et al., 2004). Research examining potential sources and concentrations of 8 phthalates in different age groups reported that infants had higher daily exposures to phthalates than adults (Wormuth et al., 2006). A Canadian study estimated that daily exposure to DEHP through multiple sources, such as plasticizers, food packaging, plastic toys and adhesives, was 9 μg/kg body mass/day in infants, 19 μg/kg body mass/day in toddlers, 14 μg/kg body mass/day in children, and 6 μg/kg body mass/day in adults (Heudorf et al., 2007). These findings suggest that infants, toddlers and children have higher levels of exposure to phthalates than adults. These higher levels of exposure could be due to higher rates of hand-to-mouth activity, increased food/water requirements per unit body mass, and higher ventilation rates.

Studies that have investigated the association between prenatal and early childhood exposure to phthalates, measured via urinary metabolites and neurodevelopmental outcomes, have not reported consistent results. The measures used to assess cognitive and behavioural outcomes of children exposed to phthalates differed among studies, which could account for the inconsistency in the results (Oleckno, 2008). To obtain a better understanding of the impact of phthalates on children's neurodevelopment, we utilized a systematic review methodology to investigate the association between phthalate metabolites and behavioral and cognitive outcomes in children 0–12 years of age. We hypothesized that higher levels of exposure to phthalates, quantified by urinary metabolite concentrations, would be associated with greater behavioral and cognitive impairment in children 0–12 years of age.

2. Methods

2.1. Search strategy

This systematic review was conducted according to a predetermined protocol and established guidelines for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000). This protocol was used in place of the PRISMA protocol, as all of the studies included in this review were observational and not randomized controlled trials. The population of interest was children aged 0–12 years. Neurodevelopmental outcomes included measures of cognition (e.g., intelligence, memory), internalizing behaviors (e.g., anxiety, depression) and externalizing behaviors (e.g., aggression). The search strategy was based on input from the coauthors, key articles, and consultation with a medical librarian with systematic review expertise. No restrictions were placed on time of publication or language. The search was executed on February 21st, 2014. The online databases searched were MEDLINE (1948–2013), PubMed (1997–2013), EMBASE (1980–2014), PsycINFO (1806–2013), CINAHL (1982–2013), Global Health (1910–2013), CAB abstracts (1910–2013), ERIC (1966–2013) databases (Fig. 1) using the key words "children (0–12 years old)" and "phthalates".

References were exported and managed using EndNote X7. We restricted our search to human studies. Bibliographies of included articles and proceedings of relevant conferences (American Psychiatric Association, American Academy of Neurology, and Pediatric Academic Societies) were manually searched for additional articles. An expert in pediatric neuropsychology (Dr. Deborah Dewey) was asked to identify any missing key publications and

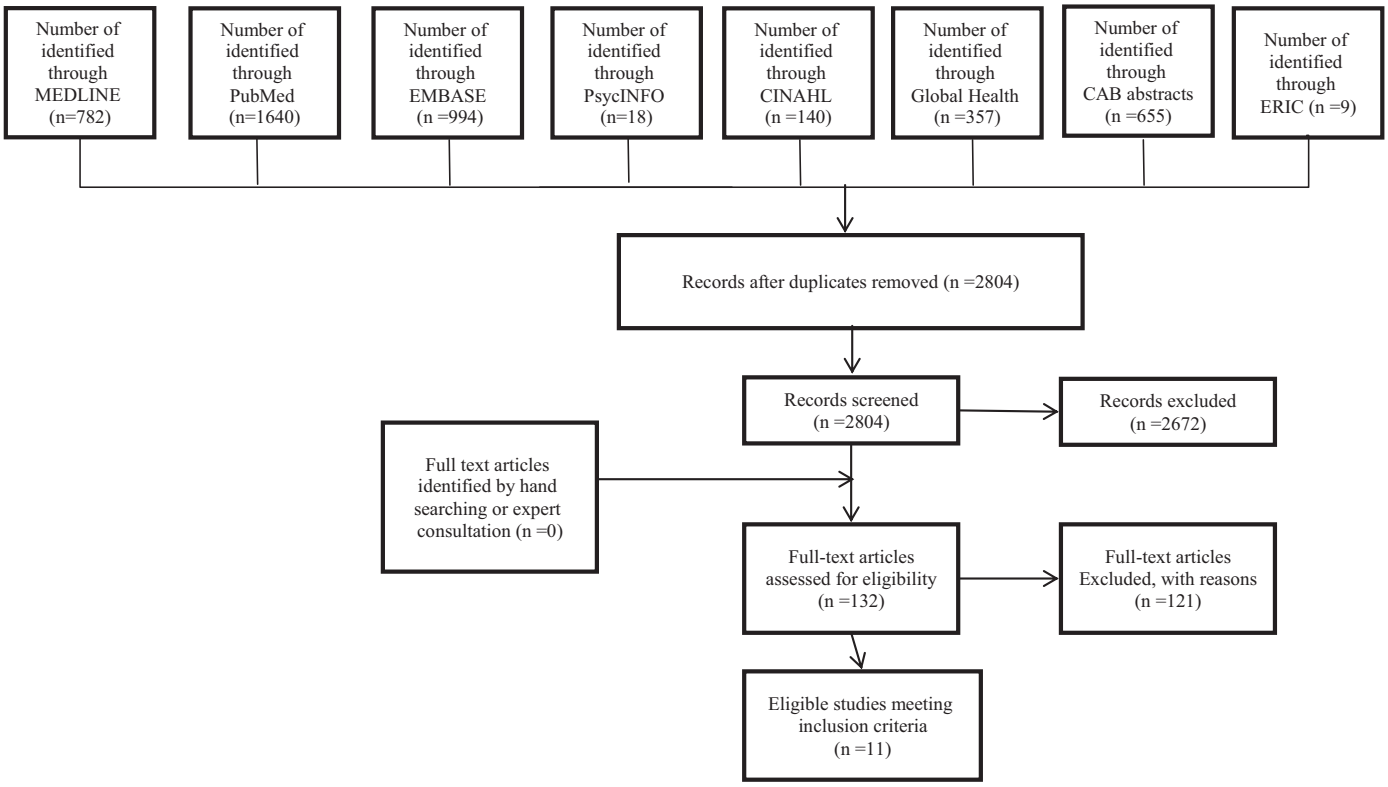

Fig. 1. Flow chart of the systematic review process, using MOOSE guidelines.

provide information on unpublished or ongoing studies. Grey literature was searched on the Health Canada (http://www.hc-sc.gc.ca/ahc-asc/pubs/index-eng.php), World Health Organization (http://www.who.int/en) and FDA (http://www.fda.gov/) websites to identify relevant missed articles.

Studies that met the following criteria were included: (1) original human study, (2) explicit mention of phthalate metabolites concentrations measured in urine (3) children 0–12 years of age, and (4) valid and standardized measures used to assess children's neurodevelopmental outcomes. Three reviewers (M.E, E.N and K. T.) independently screened the titles and abstracts of original research associated with phthalates exposure and children's neurodevelopment and behavior. Full length published studies, abstracts and unpublished studies were screened and those that met the following criteria were included in this review: (1) original research, (2) observational study design, and (3) adjusted mean differences from regression model for cognitive or behavioral outcomes were reported for children in whom phthalate metabolite urinary concentrations were measured. Disagreements regarding eligibility were resolved through discussion and involvement of a third party (Dr. Dewey), as necessary. If one article overlapped with another, we included the latest version or the better quality article.

2.2. Data extraction

A search of the included databases was performed with the population and exposure keywords. The first Boolean search was done using the terms “or” to explode (search by subject heading) and map (search by keyword) the following MeSH headings: “Child” or “Preschool” or “Infant” or “Newborn” or “Toddler” or “School age”. The second Boolean search was done by using the term “or” to explode and map “Phthalates” or “Endocrine disruptors”. The two Boolean searches were combined by using the Boolean term “and”. The search included all observational (i.e., cohort, case-control and cross-sectional) studies. From the studies

Table 2
Characteristics of studies included in the systematic review.

Source	Study	Original sample	No of participants	Country
Cho et al. (2010)	Cross-sectional	$n=667$	$n=658$	Republic of Korea
Engel et al. (2009)	Mount Sinai Children's Environmental Health (Cohort)	$n=404$	$n=311$	USA
Engel et al. (2010)	Mount Sinai Children's Environmental Health (Cohort)	$n=404$	$n=177$	USA
Kim et al. (2009)	Cross-sectional		$n=261$	Republic of Korea
Kim et al. (2011)	Mothers and Children's Environmental Health Study (MOCEH)		$n=460$	Republic of Korea
Miodovnik et al. (2011)	Mount Sinai Children's Environmental Health (Cohort)	$n=404$	$n=137$	USA
Swan et al. (2010)	Study for Future Families (SFF)	$n=334$	$n=145$	USA
Tellez-Rojo et al. (2013)	Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT)		$n=135$ $n=136$	Mexico
Testa et al. (2012)	Case-control		$n=48$	Italy
Whyatt et al. (2012)	Columbia Center for Children's Environmental Health (CCCEH)	$n=727$	$n=319$	USA
Yolton et al. (2011)	Health Outcomes and Measures of the Environment (HOME)		$n=355$	USA

identified, the following data were extracted: study information (author, year), population demographics (age, gender, location, time of data collection), condition information (condition definition, total number of participants), and confounders and/or covariates.

2.2.1. Analysis plan

Phthalates exposure was defined as a quantitative measure of the concentration of phthalate metabolites in urine samples, while neurodevelopmental outcomes were measured by children's performance/ratings on standardized cognitive and behavioural measures [e.g., Bayley Scales of Infant Development II (BSID-II), Behavioral Assessment System for Children-2 (BASC-2)]. Statistical significance was defined as 95% confidence intervals (CI) or *p*-values $< .05$ in the original articles.

3. Results

3.1. Identification and descriptive analysis

Using the MOOSE guidelines, a total of 2804 citations were identified. Of these, 11 articles were identified as meeting our criteria for inclusion in this systematic review (Fig. 1). Due to the many different phthalate metabolites examined (e.g., MBP, MEP, DEHP), the time when the metabolite samples were collected (i.e.,

Table 3
Associations between urinary concentration of low molecular weight phthalates (LMW), and children's neurodevelopmental, behavioral and cognitive outcomes.

Source	Findings
Cho et al. (2010)	Overall: Negative association between *childhood* metabolites levels of MBP and Wechsler Intelligence Scale for Children WISC
Engel et al. (2010)	Overall: Negative association between *prenatal* (25–40 weeks) urinary concentrations of MBP and level of aggression Negative association between *prenatal* (25–40 weeks) urinary concentrations of MBP and externalizing problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MBP and working memory Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and attention problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and conduct problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and depression Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and adaptability problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and behavioral symptom index scores Negative association between *prenatal* (25–40 weeks) urinary concentrations of MEP and emotional control scores Negative association between *prenatal* (25–40 weeks) urinary concentrations of MiBP and adaptability problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and internalizing problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and attention problems Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and depression Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and behavioral symptom index scores Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and global executive composite index scores Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and working memory Negative association between *prenatal* (25–40 weeks) urinary concentrations of MMP and initiation problems
Engel et al. (2009)	Boys: Positive association between *prenatal* (25–40 weeks) urinary concentrations of sum of LMW phthalate metabolites and motor performance
Kim et al. (2011)	Boys: Negative association between *prenatal* (36–42 weeks) urinary concentrations of MBP and MDI Negative association between *prenatal* (36–42 weeks) urinary concentrations of MBP and PDI
Kim et al. (2009)	Overall: Negative association between *childhood* urinary concentrations of DBP and number of omission Negative association between *childhood* urinary concentrations of DBP and commission errors
Miodovnik et al. (2011)	Overall: Negative association between *prenatal* (31.2 weeks) urinary concentrations of MEP and social cognition Negative association between *prenatal* (31.2 weeks) urinary concentrations of MEP and social communication Negative association between *prenatal* (31.2 weeks) urinary concentrations of MEP and social awareness
Swan et al. (2010)	Boys: Negative association between *prenatal* (28.3 weeks) urinary concentrations of MnBP and masculine composite score Negative association between *prenatal* (28.3 weeks) urinary concentrations of MiBP and masculine composite score
Whyatt et al. (2012)	Overall: Negative association between *prenatal* (33.1 weeks) urinary concentrations of MnBP and PDI Negative association between *prenatal* (33.1 weeks) urinary concentrations of MiBP and PDI Negative association between *prenatal* (33.1 weeks) urinary concentrations of MnBP and MDI Girls: Negative association between *prenatal* (33.1 weeks) urinary concentrations of MnBP and MDI Positive association between *prenatal* (33.1 weeks) urinary concentrations of MnBP and withdrawn behaviors Positive association between *prenatal* (33.1 weeks) urinary concentrations of MnBP and internalizing behaviors
Yolton et al. (2011)	Overall: Negative association between *prenatal (26 weeks)* urinary concentrations of DBP and arousal Negative association between *prenatal (26 weeks)* urinary concentrations of DBP and handling Positive association between *prenatal (26 weeks)* urinary concentrations of DBP and self-regulation

Note: Mental Development Index (MDI), Psychomotor Development Index (PDI), Attention Deficit Hyperactivity Disorder (ADHD) Autism Spectrum Disorders (ASD), dibutyl phthalate (DBP), monobutyl phthalate (MBP), monoethyl phthalate (MEP), monomethyl phthalate (MMP), monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(3-carboxypropyl) phthalate (MCPP).

Table 4
Associations between urinary concentration of high molecular weight phthalates (HMW) and children's neurodevelopmental, behavioral and cognitive outcomes.

Source	Findings
Cho et al. (2010)	Overall: Negative association between *childhood* metabolites levels of DEHP and children's Vocabulary subscale scores on the WISC Boys: Negative association between *childhood* sum of metabolites levels of DEHP and children's Vocabulary subscale scores on the WISC Negative association between *childhood* metabolite levels of MEHP and children's Vocabulary subscale scores on the WISC
Engel et al. (2009)	Girls: Negative association between *prenatal* (25–40 weeks) urinary concentrations of sum of HMW phthalate metabolites and Orientation score Negative association between *prenatal* (25–40 weeks) urinary concentrations of sum of HMW phthalate metabolites and Quality of Alertness score
Kim et al. (2011)	Overall: Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEHHP and MDI Negative association between *prenatal* (36-42 weeks) urinary concentrations of MEOHP and MDI Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEHHP and PDI Boys: Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEHHP and MDI Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEOHP and MDI Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEHHP and PDI Negative association between *prenatal* (36–42 weeks) urinary concentrations of MEOHP and PDI
Kim et al. (2009)	Overall: Negative association between *childhood* metabolites levels of DEHP and Teacher-rated ADHD scores
Swan et al. (2010)	Boys: Negative association between *prenatal* (28.3 weeks) urinary concentrations of MEOHP and masculine composite score Negative association between *prenatal* (28.3 weeks) urinary concentrations of MEHHP and masculine composite score
Tellez-Rojo et al. (2013)	Overall: No significant association Boys: Negative association between *prenatal* (27–40 weeks) urinary concentrations of MBzP and PDI Negative association between *prenatal* (27–40 weeks) urinary concentrations of MCPP and PDI Girls: Negative association between *prenatal* (27-40 weeks) urinary concentrations of MEHP and MDI Negative association between *prenatal* (27–40 weeks) urinary concentrations of MEHHP and MDI Negative association between *prenatal* (27–40 weeks) urinary concentrations of MEOHP and MDI Negative association between *prenatal* (27–40 weeks) urinary concentrations of MECPP and MDI
Testa et al. (2012)	Overall: Positive association between prenatal MEHP and ASD diagnosis
Whyatt et al. (2012)	Girls: Positive association between *prenatal* (33.1 weeks) urinary concentrations of MBzP and withdrawn behaviors Positive association between *prenatal* (33.1 weeks) urinary concentrations of MBzP and internalizing behaviors
Yolton et al. (2011)	Boys: Negative association between *prenatal (26 weeks)* urinary concentrations of DEHP and non-optimal reflexes

Note: Mental Development Index (MDI), Psychomotor Development Index (PDI), Attention Deficit Hyperactivity Disorder (ADHD) Autism Spectrum Disorders (ASD), mono (2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(3-carboxypropyl) phthalate (MCPP).

prenatally or in childhood) and the various outcome measures used in the research studies (e.g., BASC-2, BSID-II), we were unable to conduct a meta-analysis of the literature. As a result, we could not determine statistically whether significant associations existed between prenatal or childhood phthalate exposures and children's neurodevelopment. Therefore, we undertook a descriptive analysis of the research studies.

Table 2 includes information on the study characteristics of the 11 identified studies. As shown, most of these studies (eight out of eleven) used a cohort design. Table 3 summarizes the findings of the studies that examined the relationship between urinary concentration of LMW phthalate metabolites and cognitive and behavioral outcomes; Table 4 summarizes this information for high molecular weight phthalate metabolites.

3.2. Low molecular weight phthalates

Dimethyl phthlate (DMP) is metabolized and excreted as mono-methyl phathlate (MMP) (Table 1). Results of a study on a multiethnic cohort of 404 mother-infant pairs in New York City (Engel et al., 2010) reported that higher maternal urinary MMP was associated with poorer outcomes on measures of behavior and executive function in children 4–9 years of age. Specifically, higher levels of urinary MMP were associated with more attention problems, higher levels of depression, more overall internalizing problems, and poorer overall executive functions.

Dibutyl phathlates (DBP), di-n-butyl, and di-isobutyl are metabolized and excreted in urine as mono-n-butyl phthalate (MnBP) and momo-isobutyl phthalate (MiBP). These metabolites have been referred to as monbutyl phthalate metabolites (MBP) in the research literature (Table 1). Based on their performance on the NICU Network Neurobehavioral Scale (NNNS) (Lester and Tronick, 2004), Yolton et al. (2011) reported that higher maternal DBP was correlated with increased hypotonia, decreased arousal, higher regulation, decreased handling, and higher movement quality. Higher levels of urinary MBP have been associated with higher levels of aggression, more overall externalizing problems and problems in working memory (Engel et al., 2010). Kim et al. (2009) reported that higher urinary MBP in school-aged children was associated with an increase in the number of omission and commission errors on a continuous performance test, supporting an association between increased levels of MBP and attention problems. Cho et al. (2010), in a cross-sectional study of 667 school-aged Korean children 8–11 years of age, found that in boys, elevated urinary MBP was correlated with poorer performance on the Vocabulary subtest of the Wechsler Intelligence Scale for Children (WISC).

A prospective cohort study of 417 Korean mother–infant pairs

reported negative relationships between urinary concentrations of maternal MnBP and MiBP, and mental and physical developmental scores on the BSID-II (Bayley, 1993) at six months of age. This association remained significant even when maternal IQ was controlled (Kim et al., 2011). Higher urinary concentrations of MnBP and MiBP have also been correlated with poorer motor development at three years of age in a study of 296 mother–child pairs from New York City, USA (Whyatt et al., 2012). Whyatt et al. (2012) also found that prenatal exposure to MnBP was associated with delayed mental development on the BSID-II in girls at three years of age. In addition, prenatal exposure to MnBP was associated with internalizing behavioral problems such as withdrawn symptoms in girls, based on maternal reports on the Children Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001). In a small cohort study ($n=74$ boys and $n=71$ girls) that measured sexually dimorphic play behavior using a pre-school activities inventory, higher gestational urinary MnBP and MiBP were associated with less masculine parent-reported play behaviors among boys (Swan et al., 2010).

Diethyl phthalate (DEP) is metabolized and excreted as MEP in urine. Engel et al. (2010) reported that higher maternal urinary MEP was related to poorer outcomes on measures of behavior and executive function in children 4–9 years of age. Using the data from the Engel et al. study, Miodovnik et al. (2011) examined the long-term effects of prenatal exposure to phthalates on social behavior in 7–9-year-old children. Social impairments related to autism spectrum disorder were measured by maternal reports on the Social Responsiveness Scale (SRS) (Constantino and Gruber, 2005). Results indicated that higher maternal urinary concentrations of MEP were associated with an increase in autism-like behaviors in children. Specifically, higher levels of MEP were associated with greater social impairments, poorer social cognition, poorer social communication, and poorer social awareness.

3.3. High molecular weight phthalates

Benzylbutyl phthalate (BzBP) is metabolized and excreted as MBzP (Table 1). Whyatt et al. (2012) found that higher levels of maternal urinary MBzP was associated with higher levels of withdrawal and overall internalizing behaviors in girls. Diethylhexyl phthalate (DEHP) is metabolized and excreted in urine as MEHP, MEHHP, MEOHP and MECPP. Engel et al. (2009) reported a negative linear association between HMW phthalate metabolites (i.e., MBzP, MCPP and MEOHP) and quality of alertness and orientation in girls. Using NNNS, Yolton et al. (2011) found that maternal DEHP was associated with more non-optimal reflexes in boys. Kim et al. (2011) reported an inverse relationship between maternal urinary MEHHP and MEOHP and mental and physical developmental scores on the BSID-II (Bayley, 1993) at six months of age. Similarly, Tellez-Rojo et al. (2013) reported a negative relationship between maternal urinary MEHP, MEHHP, MEOHP and MECPP and the mental developmental scores on the BSID-II in girls. Cho et al. (2010) found that among boys, elevated urinary MEHP was correlated with poorer performance on the Vocabulary subtest of the WISC. Higher maternal urinary MEOHP and MEHHP have also been associated with less masculine parent-reported play behaviors in boys (Swan et al., 2010). In a cross-sectional study, Kim et al. (2009) reported an inverse association between childhood MEHP and MEOP and teacher-rated ADHD scores and thus more ADHD symptoms. Using a case-control design, Testa et al. (2012) found a positive association between prenatal MEHP and autism spectrum disorder diagnosis.

3.4. Summary of results

In summary, research suggests that higher prenatal and childhood exposure to LMW and HMW phthalates (measured in urinary metabolites) is associated with adverse development of typical reflexes, higher levels of internalizing and externalizing behaviors, social impairment, problems in executive functions, poorer performance on tests of vocabulary and alterations in play behavior (see Tables 3 and 4). The significant heterogeneity in the neurodevelopmental outcomes associated with exposure could be due to (1) the different times at which prenatal maternal urinary metabolite concentration was measured across studies, (2) the diverse cognitive and behavioral functions assessed, (3) the different ages at which the children were assessed, and (4) the type of phthalate metabolites measured.

3.5. Study quality assessment

The studies that were included in this review were examined for quality. A modified version of the quality assessment tool, designed by Hayden et al. (2006), was used to evaluate the quality of the studies included in this review (Table 5). It included the following factors: study participation, study attrition, outcome measurement, confounding measures (i.e., age, gender and maternal education) and statistical analyses. Our evaluation revealed that the quality of the studies included in this review was found to be adequate, with some limitations, which will be discussed in the

Table 5
Quality assessment of the studies included in the review.

Source	Study participants	Study attrition	Outcome measurement	Confounding	Analysis
Cho et al. (2010)	Yes	Not applicable	Yes	Partly	Yes
Engel et al. (2010)	Yes	Partly	Yes	Yes	Yes
Engel et al. (2009)	Yes	Partly	Yes	Yes	Yes
Kim et al. (2011)	Yes	Not applicable	Yes	Partly	Yes
Kim et al. (2009)	Yes	Partly	Yes	Partly	Yes
Miodovnik et al. (2011)	Yes	Partly	Yes	Yes	Yes
Swan et al. (2010)	Yes	Partly	Yes	Yes	Yes
Testa et al. (2012)	Yes	Not applicable	Yes	No	Yes
Tellez-Rojo et al. (2013)	Yes	Partly	Yes	Partly	Yes
Whyatt et al. (2012)	Yes	Partly	Yes	Partly	Yes
Yolton et al. (2011)	Yes	Partly	Yes	Yes	Yes

Note: Study participants were defined as the study sample being representative of the population of interest on key characteristics, sufficient to limit potential bias to the results. Study attrition was defined as loss to follow-up (from sample to study population) being described and not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias. Outcome measurement was defined as the outcome of interest being adequately measured in study participants to sufficiently limit potential bias. Confounding measurement was defined as important potential confounders being appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Analysis was defined as the statistical analysis being appropriate for the design of the study, limiting potential for presentation of invalid results.

Table 6
Type and level of phthalates exposure measured and measure used to assess children's neurodevelopmental outcomes.

Source	Exposure measurement time	Outcome measurement time	Phthalate type/level	Neurodevelopment measurement tool
Cho et al. (2010)	9 ± 0.7 years	9 ± 0.7 years of age	*LMW Mean (μg /L)* MnBP: 48.9 *HMW Mean (μg /L)* MEHP: 21.3, MEOHP: 18.0	KEDI-WISC
Engel et al. (2009)	25–40 weeks of gestation	1–5 days after birth	*LMW Median (μg/L)* MnBP: 36.2, MMP: 1.7, MEP: 385.8, MiBP 6.2 *HMW Median (μg /L)* MBzP: 23.8, MECPP: 35.8, MEHHP: 19.6, MEOHP: 17.9, MEHP: 6.1, MCPP: 3.4	Brazelton Neonatal Behavioral Assessment Scale (BNBAS)
Engel et al. (2010)	25–40 weeks of gestation	4 and 9 years of age	*LMW Median (μg/L)* MnBP: 36.2, MMP: 1.7, MEP: 385.8, MiBP 6.2	Behavior Rating Inventory of Executive Function (BRIEF)Behavior Assessment System for Children–Parent Rating Scales (BASC II-PRS)
Kim et al. (2009)	8–11 years	8–11 years of age	*LMW Mean (μg/dL)* MnBP: 46.7 *HMW Mean (μg /dL)* MEOHP: 23.4, MEHP: 34.0	Teacher-rated ADHD scores Computerized Measurements of Inattention and Impulsivity
Kim et al. (2011)	35.7–41.7 weeks of gestation	6 months of age	*LMW Mean (μg /L)* MnBP: 12.4 *HMW Mean (μg /L)* MEHHP: 8.9, MEOHP: 7.4	Bayley Scales of Infant Development - II (BSID-II)
Miodovnik et al. (2011)	31.2 weeks of gestation	7–9 years of age	*LMW Median (μg/L)* MnBP: 33, MMP: 1.8, MEP: 372, MiBP: 6.5 *HMW Median (μg /L)* DEHP (MEHHP & MECPP): 125	Social Responsiveness Scale (SRS)
Swan et al. (2010)	28.3 weeks of gestation	4–7 years of age	*LMW Mean (mg/dL)* MnBP (Boys): 19.4, MnBP (Girls): 23.0, MiBP (Boys): 4, MiBP (Girls): 4.1 *HMW Mean (mg/dL)* MEHP (Boys): 5.2, MEHP (Girls): 8.7, MEHHP (Boys): 16.0, MEHHP (Girls): 18.3, MEOHP (Boys): 14.3, MEOHP (Girls): 15.3	Pre-School Activities Inventory
Tellez-Rojo et al. (2013)	27–40 weeks of gestation	2–3 years of age	*LMW Mean (μg/L)* MnBP: 85.61, MMP: MEP: 138, MiBP: 2.3 *HMW Mean (μg/L)* MBzP: 3.54, MECPP: 39.65, MEHHP: 22.08, MEOHP: 14.23, MEHP: 6.56, MCPP: 1.75	Bayley Scales of Infant Development – II (BSID-II)
Testa et al. (2012)	11 ± 0.5 years	11 ± 0.5 years	*HMW Median (μg /L)* MEHP (Cases): 55, MEHP (Controls): 28	Autism spectrum disorders using Diagnostic and Statistical Manual of Mental Disorders (DSM IV)
Whyatt et al. (2012)	33.1 weeks of gestation	3 years	*LMW Mean (μg/L)* MnBP: 38.0, MiBP: 9.3 *HMW Mean (μg /L)* MBzP: 19.0, MECPP: 40.2, MEHHP: 23.0, MEOHP: 19.2, MEHP: 5.1	*LMW Mean (μg/L)* MnBP: 38.0, MiBP: 9.3 *HMW Mean (μg /L)* MBzP: 19.0, MECPP: 40.2, MEHHP: 23.0,MEOHP: 19.2, MEHP: 5.1
Yolton et al. (2011)	16 weeks of gestation 24 weeks of gestation 16 weeks of gestation 24 weeks of gestation	5 weeks	*LMW Median (μg/L)* MnBP/MBP: 24.0, MiBP: 4.5, MnBP/MBP: 20.3, MiBP: 3.6 *HMW Median (μg /L)* MECPP: 38.0, MEHHP: 26.9, MEOHP: 19.9, MEHP: 4.9, MECPP: 29.9, MEHHP: 20.4, MEOHP: 16.5, P: 4.2	NICU Network Neurobehavioral Scale (NNNS)

Low molecular weight (LMW), High molecular weight (HMW), Monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(3-carboxypropyl) phthalate (MCPP).

discussion section. All studies applied standardized methods for collection of urine samples, which were used to estimate phthalates exposure, and for assessing neurodevelopmental and behavioral outcomes (Table 6). Eight of the eleven studies were cohort studies, therefore, response rate, attrition and loss to follow up are major threats to internal validity. However, selection bias is only problematic if it is dependent on both exposure and outcome (Oleckno 2008), and thus the possibility of bias is minor. One of the eleven studies was a case-control study (Testa et al., 2012); therefore, selection of a representative control group is essential to ensure internal validity (Oleckno, 2008). Testa et al. used 45 randomly selected age- and gender-comparable outpatients as their control group, and thus, the possibility of selection bias is minimized. The other two studies were cross-sectional (Cho et al., 2010; Kim et al., 2009) and as a result, convenience-sampling methods could be source of selection bias (Oleckno, 2008).

Since level of phthalate concentration varies (Table 6) depending on method of exposure (e.g., diet), it has been suggested

Table 7
Confounding factors included in the studies of this review.

Source	Covariates/confounders
Cho et al. (2010)	Age, gender, birth weight, history of breast-feeding, residential area, paternal education, SES and maternal IQ
Engel et al. (2009)	Educational level of the primary caretaker, marital status of the primary caretaker, gender, race, and urinary creatinine
Engel et al. (2010)	Maternal age, maternal education, marital status, race, smoking, alcohol, caffeine, illicit drug use during pregnancy, examiner, urinary organophosphate metabolite concentration, cesarean delivery, delivery anesthesia, infant age at examination, gender, infant jaundice and urinary creatinine
Kim et al. (2009)	Maternal age, maternal education, family income, residential area, breast-feeding practices, infant birth weight, gender and maternal intelligence for subgroup analysis
Kim et al. (2011)	Parental education level, socioeconomic status, children's IQ, age, gender
Miodovnik et al. (2011)	Maternal age, maternal education, maternal IQ, marital status, child race, gender, child IQ, exact age at examination, and urinary creatinine.
Swan et al. (2010)	Maternal age, gender and age of child, parental education, number of the same and opposite gender siblings, ethnicity, clinic location and parental attitude and urinary creatinine
Tellez-Rojo et al. (2013)	Maternal age, maternal educational level, breast-feeding practices, gender, age of the child and birth weight
Testa et al. (2012)	None
Whyatt et al. (2012)	Maternal education, prenatal environmental tobacco smoke, year and season of urine collection, and umbilical cord lead and chlorpyrifos, mother's satisfaction, maternal demoralization, gender, child's age in months at test administration, and urine specific gravity
Yolton et al. (2011)	Maternal race, household income, marital status, maternal depression, maternal body mass index (BMI) at 13–19 weeks gestation, maternal blood lead level during pregnancy, reported alcohol use during pregnancy, reported marijuana use during pregnancy, maternal serum cotinine (a measure of tobacco smoke exposure) during pregnancy, and infant weight change per month from birth to five weeks, infant age in days at the time of exam, gender, birth weight less than 2500 g, stay in the NICU following birth

that one-time measurement of phthalate exposure may not accurately assess level of exposure. Thus, the number of times phthalates exposure is assessed (one versus multiple urine samples) could bias the estimates of exposures. In addition, the use of parent-report measures could result in in misclassification of neurodevelopmental outcomes due to parents either under-reporting (e.g. due to social stigma) or over-estimating (e.g., due to desire to have access to special services) their children's neurodevelopmental problems, (e.g. Engel et al., 2010; Swan et al., 2010). Existence of selection or measurement biases, weaken the internal validity of the included studies. Ten of the eleven studies identified, adjusted for potential confounders; however, the number of confounding variables varied among studies (Table 7). Controlling for confounding factors minimizes the magnitude of the distortion of the reported associations (Oleckno, 2008). However, due to diversity among the number and type of the included confounding factors among studies, the findings should be pooled with caution.

4. Discussion

This systematic review suggests that higher levels of prenatal exposure to phthalate metabolites measured as urinary concentrations are associated with poorer cognitive and behavioral outcomes in children 0–12 years of age. This is consistent with previous research. In addition, this review also reveals sex-specific differences in cognitive and behavioral functions. Of the nine studies that examined the relationship between urinary concentrations of LMW phthalate metabolites and children's cognitive and behavioral outcomes, four reported adverse outcomes among boys, whereas only one found adverse outcomes in girls (Table 3). Of the nine studies that examined the relationship between urinary concentrations of HMW phthalate metabolites and children's neurodevelopment, four studies noted adverse outcomes among boys, whereas only two reported adverse outcomes in girls (Table 4). These findings suggest that exposure to endocrine disrupting phthalate metabolites alter children's neurodevelopment and that exposure places boys are higher at risk for poorer neurodevelopmental outcomes.

4.1. Strengths and limitations

This study has several strengths. To our knowledge, this is the first systematic review that investigated the relationship between prenatal phthalates exposure and cognitive and behavioral outcomes in children. Most of the human studies included in this review were cohort studies, therefore, response rate, and loss to follow up are major threats to internal validity (Oleckno, 2008). Since all of the studies included reported high response rates and the probability of selection was not dependent on both exposure and outcome, the possibility of selection bias is minimized. Also, all of the included studies used biomarkers to estimate level of phthalates exposure (measured as urinary metabolites) and standardized cognitive and behavioral assessment tools to measure outcome. Thus, the possibility of measurement bias by both exposure and outcome were decreased. Third, different studies examined different confounding factors and adjusted for them (Table 7). The inclusion of adjusted values, however, minimizes the magnitude of the distortion of the reported estimates. Fourth, the results from human studies are consistent with previous animal research, which has reported neurodevelopmental impairments (Betz et al., 2013; Hoshi and Ohtsuka, 2009; Li et al., 2013). Finally, as phthalates disrupt the endocrine system by binding to androgens, which mediate the development of sex-specific behaviors, including aggression and anxiety (Patisaul and Polston, 2008), our findings of sex differences in cognitive and behavioral outcomes in children exposed prenatal exposure are biologically plausible.

This systematic review has some limitations. Several of the published studies included used the same cohort and the datapoints to examine neurodevelopmental outcomes; as a result the studies were not independent of each other and could not be included in a meta-analysis. A second limitation is that some studies used a single urine sample to assess phthalates exposure. This could reduce the accuracy of phthalates measurement and could result in biased phthalate estimates. Moreover, the studies used different adjustment methods (creatinine or specific gravity) to measure urinary phthalate concentrations, and this could also result in measurement bias. It is noteworthy that, with the exception of the HOME study, none of the cohort studies included in this review were primarily designed with phthalate exposure assessment in mind. Thus, samples were likely stored, thawed, and refrozen multiple times, which could also result in measurement bias. Finally, as parents may underestimate or overestimate their child′s neurodevelopment (Oleckno, 2008), the parent-report measures could result in measurement bias (Engel et al., 2010; Swan et al., 2010). The use of multiple measurement tools, which include parent-report measures and measures of children′s performance (Dietrich et al., 2005), could minimize the possibility of

measurement bias.

Differences among studies in cognitive and behavioral outcomes of the children could be attributed to different levels of exposure and differences in the age of the children at the time of the neurodevelopmental assessment. Thus, the possible modifying role of level of exposure and age at time of assessment needs to be investigated. The sample size used in the studies included in this systematic review ranged from an *n* of 460 (Kim et al., 2011) to an *n* of 135 (Tellez-Rojo et al., 2013). As none of the reviewed studies included sample size calculations, inadequate sample size may have increased the chance of a Type II error (Oleckno, 2008). Furthermore a significant proportion of the studies (six out of eleven) were conducted in the United States. Consequently, these findings may have low generalizability to future studies conducted outside of the United States, if different levels of phthalates exposure are found prenatally in the populations of children studied. Finally, for case-control and cross-sectional studies (3 of the 11 studies), temporality (i.e., exposure precedes outcome) cannot be established.

4.2. Future directions and implications

This study identified some inconsistencies in the literature. The significant heterogeneity in the neurodevelopmental outcomes associated with phthalates exposure could be due to: (1) the varied times at which prenatal maternal exposure was measured across studies, (2) the diverse cognitive and behaviour functions assessed, (3) the different ages at which the children were assessed, and (4) the type of phthalate metabolites measured. Well-designed cohort studies are needed to explore the relationship between prenatal and childhood exposure to various phthalate metabolites and children's neurodevelopment.

At present, to the best of our knowledge, no public policies have been implemented that limit exposure of pregnant women, nursing mothers, and children to phthalates. To better understand the etiology of neurodevelopmental disorders, the effects of endocrine disrupting chemicals, such as phthalates, on neurodevelopment, need to be explored in human populations. Educating pregnant women about sources of exposure could result in reduced levels of exposure and could limit the potential harmful effects on children′s neurodevelopment. Though identifying the role of these chemicals in neurodevelopmental disorders may be very challenging, limiting the amount of exposure through various public policy initiatives could provide us with an exceptional opportunity to reduce the prevalence of neurodevelopmental disorders.

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