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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