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# The effects of maternal and children phthalate exposure on the neurocognitive function of 6-year-old children[☆]

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## ABSTRACT

The primary purpose of this study was to investigate the effects of phthalate exposure on the intelligence and attentional performance of 6-year old children when adjusting each other as covariates. We also investigated the differential effects of phthalate exposure on the intelligence and attention according to exposure period (maternal or children). Urine concentrations of mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-n-butyl phthalate (MBP) were analyzed. Multivariable linear regression models were used to investigate the relationship between exposure to various phthalates with IQ scores and continuous performance test (CPT) variables. There were robust associations between child MEHHP and MEOHP levels with full scale IQ (FSIQ) even after adjusting for demographic variables and CPT scores (MEHHP −9.27, 95% CI: −17.25, −1.29; MEOHP −9.83, 95% CI: −17.44, −2.21). Child MEHHP and MEHOP levels negatively affected omission errors (MEHHP −20.36, 95% CI: −34.17, −6.55; MEOHP −18.93, 95% CI: −32.58, −5.28) and the response time variability (MEHHP −21.07, 95% CI: −39.04, −3.10; MEOHP −20.41, 95% CI −38.14, −2.69) of the CPT after adjusting for demographic variables and IQ. Maternal phthalate exposure had no effects on IQ or CPT variables. These results suggest that children phthalate exposure, but not maternal exposure, has an adverse effect on IQ and attentional performance, and these associations were found to be independent of each other.

## 1. Introduction

Phthalates are endocrine-disrupting chemicals widely used in commercial products as plasticizers for polyvinyl chloride and as solvents in personal care products (Sathyanarayana, 2008). Phthalate-containing products include cosmetics, plastics, carpets, building materials, toys, and medical and cleaning products (Miodovnik et al., 2014). These materials are divided into two distinct groups according to their molecular weight and chemical properties. Low-molecular-weight phthalates, such as di-n-butyl-phthalate (DBP), are used in personal care products such as cosmetics and lotion, and ubiquitous daily exposure is expected as a result (Braun et al., 2013; Ejaredar et al., 2015). High-molecular-weight phthalates, such as di (2-ethylhexyl) phthalate (DEHP) are mainly used as plasticizers and adhesives. Diet is the most likely exposure route for high-molecular-weight phthalates, as these compounds can leach from containers into food products over time (Bornehag et al., 2005; Carlstedt et al., 2013). Recent studies have shown high levels of exposure to phthalates, DEHP in particular, in

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*Abbreviations:* DBP, di-n-butyl-phthalate; DEHP, di (2-ethylhexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBP, Mono-n-butyl phthalate; FSIQ, full-scale intelligence quotient; CPT, continuous performance test; RTV, response time variability; AQs, attention quotients

[☆] The study protocol was reviewed and approved by the Institutional Review Board of the Seoul National University Hospital.

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neonates and children admitted to intensive care units (ICU), which is likely because DEHP is used as a plasticizer in a variety of medical products, including intravenous fluid bags, tubes, and catheters (Weuve et al., 2006).

Phthalates are metabolized rapidly into monoesters, which can be further transformed into more hydrophilic oxidative metabolites that are eliminated mainly via urine. Secondary oxidized DEHP metabolites include mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), which are valuable markers of DEHP exposure. Mono-n-butyl phthalate (MBP) is a metabolite of DBP and is used as a biomarker of DBP exposure. Epidemiologic studies measure phthalate metabolites in urine as internal dosimeters of exposure, because urine enzymatic activity is negligible and the metabolites predominantly arise from elimination of endogenous phthalates, rather than from external contamination with phthalates during collection and processing (Kato et al., 2004). Previous studies demonstrate that exposure to phthalates during hospitalization in ICUs can lead to long-term attention deficit even up to years after discharge (Verstraete et al., 2016).

Evidence suggests that phthalates interfere with the thyroid hormone system (Ghisari and Bonefeld-Jorgensen, 2009), which is critical to normal brain development in the fetus and infant (Berbel et al., 2010). A growing body of evidence has shown that phthalate exposure impairs neurodevelopment in children. For example, DEHP and DBP exposure resulted in impaired pup learning, memory, and brain development (Arcadi et al., 1998; Li et al., 2013; Tanida et al., 2009). In addition, prospective studies have demonstrated adverse effects of prenatal phthalate exposure using child Bayley scale scores at 6 months and 3 years of age (Kim et al., 2011; Whyatt et al., 2012). In addition, Kim et al. and Park et al. examined the effects of phthalate metabolites on attentional performance in community samples and attention deficit hyperactivity disorder (ADHD) clinical samples, respectively (Kim et al., 2009; Park et al., 2014).

Studies on the impact of phthalates according to the time of exposure (i.e., prenatal or postnatal) on childhood intelligence quotient (IQ) scores have produced mixed results. Cho et al. was the first to report that DEHP metabolites measured at school age were negatively associated with full scale IQ (FSIQ) and verbal IQ scores, but this association was not significant after adjusting for maternal IQ. Only the relationship between DEHP metabolites and the vocabulary subscale score remained after adjusting for maternal IQ (Cho et al., 2010). One study on the association between prenatal phthalate exposure and IQ reported that prenatal DBP and diisobutyl phthalate exposure were inversely associated with FSIQ at age 7 (Factor-Litvak et al., 2014), but another longitudinal study reported that phthalate exposure in children, but not prenatal exposure, was associated with decreased IQ scores (Huang et al., 2015).

Another limitation of previous studies on the relationship between phthalates and IQ is that they have not controlled for other neurocognitive factors that may impair performance on IQ testing, such as attention. Various studies have reported on the effects of phthalate exposure on attentional performance measures using the continuous performance test (CPT) (Kim et al., 2009; Park et al., 2014). Given that poor attentional performance may interfere with intelligence test performance (Biederman et al., 2011), it would be reasonable to control for concurrent attention and behavioral problems when estimating the association between phthalate exposure and intelligence. Hong et al. emphasized the importance of adjustment in a study on the relationship between lead exposure with IQ and ADHD symptoms, as children with ADHD may have a higher chance of having been exposed to lead, which would be responsible for their lower intelligence (Hong et al., 2015).

This study addressed important issues that have not been clarified. The primary purpose was to investigate whether environmental phthalate exposure was associated with both reduced intelligence and attentional performance when adjusting each other as covariates. The secondary purposes were to investigate whether the association between child IQ and phthalate exposure was influenced by maternal IQ and also to determine the effect of time of exposure on neurocognitive development by assessing the effects of both maternal (prenatal) and children (postnatal) exposure.

## 2. Materials and methods

### 2.1. Participants

This study was conducted as part of an on-going cohort named “The Environment and Development of Children”, which has the purpose of observing the growth and development of the offspring of pregnant women who enrolled between 2008 and 2011. From 2012 to 2013, 645 mother–child pairs were enrolled to participate after contacting 2085 mothers (response rate, 30.9%). The parents completed a survey on socioeconomic factors (e.g., parental education level and monthly family income) and medical history (e.g., history of surgery, head trauma, or other medical disorders). Information on gestational factors (e.g., birth weight and gestational age at birth) was obtained by medical records. Children underwent IQ and CPT tests when they reached the age of 6, and among the 645 children recruited, 182 children conducted these tests during the period of April 2015 to December 2015. Six children without IQ scores or CPT data were excluded, and one child who had epilepsy and was currently taking anti-epileptic medication was excluded, leaving a total of 175 participants to be analyzed in this study.

Detailed information on the study was provided to all parents of the participants, and written informed consent was obtained prior to enrollment. The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital.

### 2.2. Measurement of neurocognitive function

A Korean version of a computerized CPT called the Comprehensive Attention Test was administered, which has established reliability and validity (Yoo et al., 2009). We used the visual selective attention task, in which various shapes appear on the monitor in 2-sec intervals and the participants are instructed to press the buzzer as fast as possible when a circle appears. Performance was assessed for four variables: (1) omission errors (failure to respond; measurement of inattention), (2) commission errors (faulty response; measurement of impulsivity), (3) response time (mean time of correct responses; measurement of processing speed), and (4) response time standard deviation (standard deviation of response time for correct responses; measurement of response time variability [RTV]). All scores were transformed into attention quotients (AQs), which were adjusted for age and gender by comparison to a normal population with an average AQ of 100 and standard deviation of 15. Higher AQ scores indicated better performance; an AQ score below 76 ($>1.6$ SD) was indicative of poor performance, a score of 76–85 ($>1$ SD and $<1.6$ SD) indicated borderline performance, and a score above 85 ($<1$ SD) indicated normal performance.

Child IQ was measured using the Korean Educational Developmental Institute's Wechsler Intelligence Scale for Children (Park et al., 1996), which is divided into four subtests: vocabulary, arithmetic, picture arrangement, and block design. The sum of the first two subtests’ age-adjusted scaled scores estimates verbal IQ, and the sum of the latter two subtests’ scores estimates performance IQ. The mother's IQ was assessed using the short form of the Korean Wechsler Adult Intelligence Scale (Lim et al., 2000). IQ calculated from the short form correlates well with the full scale (FSIQ) (Silverstein, 1990).

### 2.3. Measurement of phthalate metabolites

Maternal phthalate metabolite levels were measured using maternal urine in the second trimester of pregnancy between 14 and 27 weeks