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Concentrations of phthalate metabolites in breast milk in Korea: Estimating exposure to phthalates and potential risks among breast-fed infants

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HIGHLIGHTS

- Metabolites of DEHP, DnBP, DiBP and DEP were detected in >79% of breast milk samples.
- MEHP level was comparable to, but MEP was lower than that reported elsewhere.
- 6–8% of infants showed hazard quotients >1 by DnBP or DEHP in breast milk.

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ABSTRACT

Phthalates have been associated with endocrine disruption and developmental effects in many experimental and epidemiological studies. Developing infants are among the most susceptible populations to endocrine disruption. However, limited information is available on phthalate exposure and its associated risks among breast-fed newborn infants. In the present study, breast milk samples were collected from 62 lactating mothers at 1 month post-partum from four cities of Korea in 2012 and were evaluated for six phthalate metabolites (mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), mono(2-ethyl-hexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) and monoethyl phthalate (MEP)). MEP was detected in all breast milk samples, with a median concentration of 0.37 μg/L, and MiBP, MnBP and MEHP were detected in 79–89% of samples, with median concentrations of 1.10, 1.70, and 2.08 μg/L, respectively. However, MEHHP and MEOHP, the oxidized forms of di-ethyl-hexyl phthalate (DEHP), were detected in only one sample. For exposure assessment, the levels of phthalate diesters were estimated based on the parent:metabolite ratios in the breast milk that are reported elsewhere. For risk assessment, the endocrine-related toxicity of the monoester was assumed to be the same as that of its diester form. Median daily intake estimates of phthalates, including both monoester and diester forms, through breast milk consumption ranged between 0.91 and 6.52 μg/kg body weight (bw) for DEHP and between 0.38 and 1.43 μg/kg bw for di-n-butyl phthalate (DnBP). Based on the estimated daily intake, up to 8% of infants exceeded the reference dose of anti-androgenicity (RfD AA) for DEHP, and 6% of infants exceeded the tolerable daily intake (TDI) for DnBP. Breast milk MiBP and MnBP concentrations showed significant positive associations with maternal consumption

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of whipped cream or purified water. Considering vulnerability of young infants, efforts to mitigate phthalate exposure among lactating women are warranted.

1. Introduction

Phthalates have been used in various consumer products, such as vinyl tiles, food processing materials, medical devices, plastic bags, toys, and personal care products. Because phthalates are not chemically bound to the products, these compounds can be easily released into the surrounding environment, including air, water, or dust (CDC, 2009), leading to exposure among humans. Phthalates and their metabolites have been frequently detected in human urine and serum samples worldwide (Calafat and McKee, 2006; Guo et al., 2011; Koch et al., 2003; Silva et al., 2004; Song et al., 2013).

Phthalate exposure has been associated with endocrine disruption, reproductive developmental damage, neurodevelopmental toxicity, and growth-related problems in several experimental studies (Andrade et al., 2006; Borch et al., 2004; Gray et al., 2000; Okubo et al., 2003; Xu et al., 2005). In humans, di-ethyl-hexyl phthalate (DEHP) and di-n-butyl phthalate (DnBP) have also been related to disruption of sex hormone balance (Lovekamp-Swan and Davis, 2003; Pan et al., 2006). Additionally, a decrease in sperm quality was associated with diethyl phthalate (DEP) and DEHP exposure (Duty et al., 2004; Hauser et al., 2007). Because of rapid cellular differentiation and incomplete metabolic system, the fetus and infant are generally considered to be more vulnerable to endocrine-disrupting chemicals (Birnbaum, 1994). Endocrine disruption and neurodevelopmental toxicity by phthalate exposure are therefore more important during the early stages of life. Although caution is warranted in direct interpretation of these observations, prenatal exposure to phthalates such as DEHP or DnBP has been often associated with adverse mental and motor development (Kim et al., 2011; Whyatt et al., 2012) and decreased IQ scores (Cho et al., 2010) in children.

Breast-feeding rates vary across countries but generally range between 61 and 98% (WHO, http://www.who.int/nutrition/databases/infantfeeding/countries/en/). For example, the breast-feeding rate in Korea was 81% in 2003 (Chung et al., 2008). Because it is often the only major source of nutrition, breast milk could serve as the most important medium of exposure to various environmental contaminants among young infants (Shea, 2003). However, the presence of phthalate metabolites in breast milk has not been extensively investigated. For example, no information is currently available on the breast milk levels of phthalate metabolites in Korea. Monitoring the levels of phthalate metabolites in breast milk is crucial to understanding the phthalate exposure among breast-fed infants and to estimating associated risks.

However, analyzing phthalate metabolites in breast milk is challenging because of possible contamination of phthalate diesters and their subsequent hydrolytic conversion to monoesters. Unlike urine, breast milk contains hydrolyzing enzymes; therefore, phthalate monoesters detected in the breast milk could possibly originate from the external contamination of diesters (Calafat et al., 2004, 2013). Therefore, measures to prevent potential contamination of phthalate diesters and to inhibit hydrolytic enzyme activities are necessary to ensure reliable measurements of phthalate monoesters in breast milk (Fromme et al., 2011).

In the present study, we collected breast milk samples from lactating women who had participated in the 'Children's Health and Environmental Chemicals in Korea (CHECK)' Panel at 1 month post-delivery. The CHECK Panel consists of pregnant woman and matching newborn infant pairs from four cities of Korea, and participants have been followed since 2011 for chemical exposures and adverse health effects (Choi et al., 2014; Kim et al., 2013). In this study, we (1) measured the levels of six metabolites of four major phthalates in breast milk, (2) estimated the daily intake of phthalates among breast-fed infants and associated risks, and (3) investigated potential sources of phthalate exposure to breast milk. This study will help understand the importance of breast milk as a source of phthalate exposure among newborn infants and provide baseline data to develop management options for early life stage exposure to phthalates.

2. Materials and methods

2.1. Study population and sample collection

Breast milk samples were collected from breast-feeding mothers (n = 62) at one month after delivery. Participating lactating women had been recruited before delivery at five university hospitals located in four cities of Korea (Seoul, Anyang, Ansan, and Jeju) during April–October 2012. One-on-one interviews with participating pregnant women were conducted at the time of enrollment. Demographic parameters, physiological data, pregnancy history and the gestational period of the current delivery, and previous medical records were obtained. At the time of breast milk sampling, another questionnaire survey was conducted for dietary characteristics and cosmetic use, but the survey was conducted with only 25 women. The breast milk consumption rate of each newborn infant was measured by the weighing method at one month after delivery and was reported in Lee et al. (2013). Participating women were between 23 and 46 years of age (mean 33 years), and the pre-pregnancy body mass index (BMI) ranged between 16.0 and 30.1 kg/m^2 (mean 21 kg/m^2) (Table 1). Breast milk was collected in polypropylene tubes by hand expression on the 30th day after delivery following the detailed sampling protocol. All of the polypropylene tubes provided had previously been washed by acetonitrile, methanol and acetone. The breast milk samples were frozen immediately after collection and later transported on ice to the laboratory. Upon delivery, the samples were subsequently stored at −70 °C until analysis. Institutional Review Boards of the School of Public Health, Seoul National University approved the study, and informed consent was obtained from the participating women. All samples and data were processed blindly.

2.2. Chemical analysis

Six major metabolites of four phthalates (mono-isobutyl phthalate (MiBP) of di-isobutyl phthalate (DiBP); mono-n-butyl phthalate (MnBP) of DnBP; mono(2-ethyl-hexyl) phthalate (MEHP), mono-(2-

Table 1
Characteristics of the study population.

Variable	Range	Mean	SD	Median
Pregnant women (n = 62)				
Age (year)	23–46	33	4.6	34
Pre-pregnancy BMI (kg/m^2)[a]	16.0–30.1	21.0	2.5	20.3
Parity[a]	0–3	1	0.8	1
Gestational age at delivery (days)	260–290	276	7.1	276
Infants (n = 62)				
Sex	Male: 29, female: 33			
Birth weight (kg)[b]	2.5–4.4	3.3	0.3	3.3
Weight at 1 month of age (kg)	3.0–7.2	4.5	0.8	4.5
Breast milk consumption amount per day (mL/d)	70–1440	709	196	704

[a] Parity as birth history. For primipara, '0' was given.
[b] Because of missing data, BMI is based on 58 women, weight of infants at 1-month of age is based on 47 infants, and breast milk consumption amount is based on 24 infants.