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Interaction of melamine and di-(2-ethylhexyl) phthalate exposure on markers of early renal damage in children: The 2011 Taiwan food scandal

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ABSTRACT

Melamine and phthalate, mainly di-(2-ethylhexyl) phthalate (DEHP), are ubiquitously present in the general environment. We investigated whether urine melamine levels can modify the relationship between DEHP exposure and markers of early renal damage in children. A nationwide health survey for Children aged ≤12 years possibly exposed to phthalates were enrolled between August 2012 and January 2013. They were administered questionnaires to collect details regarding past DEHP exposure to phthalate-tainted foodstuffs. Urine samples were measured melamine levels, phthalate metabolites and biomarkers of renal damage, including urine microalbumin/creatinine ratio (ACR), N-acetyl-beta-D-glucosaminidase (NAG), and β2-microglobulin. The study included 224 children who had a median urine melamine level (μg/mmol creatinine) of 1.61 ranging 0.18–47.42. Positive correlations were found between urine melamine levels and urine ACR as well as urine NAG levels (both Spearman correlation coefficients $r = 0.24$, $n = 224$, $p < .001$). The higher the past DEHP exposure or urine melamine levels, the higher the prevalence of microalbuminuria. An interaction effect was also found between urine melamine levels and past DEHP exposure on urine ACR. Melamine levels may further modify the effect of past DEHP exposure on urine ACR in children.

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1. Introduction

The 2008 melamine baby formula scandal in China caused kidney-related diseases and kidney failure in children (Ingelfinger, 2008). Although the threat of added melamine to baby formula subsided, we should be reminded that the chemical melamine remains ubiquitously present in our environment (Ingelfinger, 2008; Panuwet et al., 2012; Lin et al., 2013). It has been detected in most urine samples obtained from the general populations of the USA and Taiwan, where chronic low-dose exposure to environmental melamine has been associated with risk of renal stone formation and early renal damage (Wu et al., 2010, 2015; Liu et al., 2011).

News of another food scandal, one involving phthalate-tainted food, broke out in Taiwan in 2011 (Wu et al., 2012). Phthalates, mainly di-(2-ethylhexyl) phthalate (DEHP), were intentionally added to a variety of foodstuffs, including multiple vitamins and probiotics, regularly taken by infants and children as nutrient supplements (Wu et al., 2012, 2013a,b, 2014; Tsai et al., 2016a,b). One of our recent studies found that DEHP may be associated with a higher prevelance of microalbuminuria in children exposed daily to

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higher amounts of phthalate-tainted foods (Tsai et al., 2016a).

Although the USA and European Union established recommended tolerable daily intakes (TDIs) of common environmental chemicals such as melamine and DEHP in humans, their estimates were based largely on the results of animal experiments which they extrapolated to the humans, including sensitive subpopulations such as children (EPA 1987; EFSA 2005; WHO, 2009). Another problem with recommended TDIs is that they are usually established for one chemical alone, which is hardly the case in the real world, where people are potentially exposed to a mixture of chemical toxins. In this study, we investigated the interactive effect of two common environmental chemicals, melamine and DEHP, on biomarkers of renal injury in a unique cohort of children.

2. Materials and methods

2.1. Study participants

The slightly modified design used for this study has been described in detail in an earlier study (Tsai et al., 2016a). Briefly, we recruited children whose families had complained to the Taiwan Consumers' Foundation about their being possible victims of the phthalate-tainted foods and had filed a lawsuit for compensation between August 2012 and January 2013 (Wu et al., 2012; Tsai et al., 2016a). Those who lodged complaints and who were willing to participate in this study were referred to one of three special phthalate clinics, located in the northern, central, and southern Taiwan. The current study revisits this cohort focusing on children aged $\leq$12 yrs. After agreeing to participate in this study, the main caregiver (mostly the mother) of each child was administered a questionnaire collecting detailed information from which we could estimate each child's exposure to phthalate-tainted foods. All participants were well-being without diabetes mellitus, urinary tract obstruction and other systemic diseases. The children also received physical examinations and blood and urine workups. The measurements of all clinical and laboratory parameters have been described previously (Tsai et al., 2016a). The protocol for this study was approved by the institutional review boards (IRBs) of National Health Research Institutes (NHRI), the Ministry of Health and Welfare Hospitals (MHWHs), and Kaohsiung Medical University Hospital (KMUH). The reference number of the approvals was NHRI-EC100090 and KMUH-IRB-2012-11-01. The methods were carried out in accordance with the approved guidelines. Written informed consent was obtained from the main caregiver of each child studied.

2.2. Past DEHP exposure estimated based on intake of phthalate-tainted food items by questionnaire

Before each child received a phlebotomy, his or her main caregiver was interviewed using a standardized questionnaire to collect information on the child's consumption of any government-identified phthalates-tainted food items. The phthalate concentrations in these phthalate-tainted food items were extracted from publications produced by Taiwan's Food and Drug Administration (TFDA) and the Bureau of Health of Kaohsiung City (KBOH) (Wu et al., 2012). With this information, we were able to construct daily DEHP intake (DDI, mg/kg body weight (bw)/day) based on amount of DEHP they were exposed to (mg per time) and frequency (times per day) divided by body weight of each child (Wu et al., 2013a,b; Tsai et al., 2016a). Our previous study has demonstrated a high correlation between estimated DDI by questionnaire and oxidative DEHP metabolites in urine collected during that incident (Wu et al., 2013b). Among the 23 affected children with exposure information about that incident and the baseline of urine specimens collected during that incident, we found that the Spearmen correlation coefficient between estimated daily DEHP intake by questionnaire and by urinary oxidative DEHP metabolites using creatinine-based models was 0.466, which was significantly correlated ($p = .025$).

2.3. Urine collection

One-spot morning urine sample in each child was collected after the interview of questionnaire. Part of each sample was used for routine urinary analysis and the rest of urine sample was aliquoted and stored at −20 °C for the subsequent detection and measurement of melamine, phthalate metabolites, and biomarkers of renal injury.

2.4. Measurement phthalate metabolites in urine

We measured nine phthalate metabolites in the urine samples. The metabolites were mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-isobutyl phthalate (MiBP) and monoisononyl phthalate (MiNP), seven of which are the most common phthalates found in the environment (DEHP, DnBP, DiBP, BBzP, DMP, DEP, and DINP). Liquid chromatography/electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) was used to measure the nine phthalate metabolites in urine, following methods described in detail previously (Kuo et al., 2015; Tsai et al., 2016a). In brief, to prepare urine samples for analysis, 1 mL of each sample was thawed, transferred to a glass tube, and spiked with a mixture of isotopic (^{13}C4) phthalate monoester standards (10 μL). Then, they were buffered with ammonium acetate (250 μL, 1 M, pH = 6.5) and β-glucuronidase enzyme (3 μL, 200 U/mL), and were incubated in a 37 °C water bath for 90 min. After hydrolysis, each sample was acidified by adding 2 mL phosphate buffer (0.14 M NaH2PO4 in 0.85% H3PO4), vortex-mixed, and centrifuged at 3500 rpm for 10 min. The supernatant was loaded into a solid-phase extraction cartridge (NEXUS, Varian, Inc., Palo Alto, CA, U.S.A.). Formic acid (2 mL) and water (2 mL) were added to remove hydrophilic compounds, and then acetonitrile (1 mL) and ethyl acetate (1 mL) were added to elute metabolites. The combined elutes were concentrated under a stream of dry nitrogen at 55 °C. Finally, the residues were reconstituted with water and subjected to LC-MS/MS for analysis.

For method validation, the calibration was performed by using standard solutions of phthalate metabolites in pooled urine samples described in the previous studies (Kuo et al., 2015; Tsai et al., 2016a). The corresponding rings labeled analogs were used as internal standard (IS). The calibration range of each metabolite was divided into two: 1–50 ng/mL for the low one and 50–1000 ng/mL for the high one. The correlation coefficients (R^2) of these calibrations were 0.998–0.999 for MEHP, 0.996–0.998 for MEHHP, 0.998–1 for MEOHP, 0.994–0.998 for MnBP, 0.996–0.999 for MiBP, 0.991–0.996 for MEP, 0.993–0.999 for MBzP, 0.993–0.997 for MMP, and 0.998–1 for MiNP, which were all higher than 0.9950. Internal quality control was performed by analyzing both low (10 ng/mL) and high (100 ng/mL) levels spiked in urine in each batch. The accuracy for all calibration concentration curves and internal quality controls was within the range from 95.2 to 104.6% and with the precision expressed as a coefficient of variance (CV) ranging from 1.2 to 7.4% ($n = 5$). The intra- and inter-day relative standard deviation (RSD) ranged from 0.50 to 9.10% and 2.50–11.30% respectively. The averaged IS recovery in urine mixture was 80–115.0%, except for MEHP, MMP, and MiNP that showed IS recovery about 50%.

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