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Associations of prenatal exposure to five chlorophenols with adverse birth outcomes☆

Jianqiu Guo [a], Chunhua Wu [a, *], Shenliang Lv [a, b], Dasheng Lu [a, b], Chao Feng [b], Xiaojuan Qi [a, c], Weijiu Liang [d], Xiuli Chang [a], Hao Xu [d], Guoquan Wang [b], Zhijun Zhou [a]

[a] School of Public Health, Key Laboratory of Public Health Safety of Ministry of Education, Collaborative Innovation Center of Social Risks Governance in Health, Fudan University, No.130 Dong'an Road, Shanghai, 200032, China
[b] Shanghai Municipal Center for Disease Control and Prevention, No. 1380 Zhongshan West Road, Shanghai, 200336, China
[c] Zhejiang Provincial Center for Disease Control and Prevention, No. 3399, Binsheng Road, Hangzhou, 310051, China
[d] Changning District, Shanghai Center for Disease Control and Prevention, No.39 Yunwushan Road, Shanghai, 200051, China

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ABSTRACT

Exposures to chlorophenols (CPs) have been linked with adverse health effects on wildlife and humans. This study aimed to evaluate prenatal exposure to five CP compounds using maternal urinary concentrations during pregnancy and the potential associations with birth outcomes of their infants at birth. A total of 1100 mother-newborn pairs were recruited during June 2009 to January 2010 in an agricultural region, China. Urinary concentrations of five CPs from dichlorophenol (DCP) to pentachlorophenol (PCP), namely, 2,5-DCP, 2,4-DCP, 2,4,5-trichlorophenol (2,4,5-TCP), 2,4,6-TCP and PCP, were measured using large-volume-injection gas chromatography-tandem mass spectrometry (LVI-GC-MS-MS), and associations between CP levels and weight, length as well as head circumference at birth were examined. Median urinary creatinine-adjusted concentrations of 2,5-DCP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP and PCP were 3.34 μg/g, 1.03 μg/g, < LOD, 1.78 μg/g and 0.39 μg/g creatinine, respectively. We found lower birth weight 30 g [95% confidence interval (CI): −57, −3; $p = 0.03$] for per SD increase in $\log_{10}$-transformed concentrations of 2,4,6-TCP and lower birth weight 37 g (95% CI: −64, −10; $p = 0.04$) for PCP, respectively. Similarly, head circumference decrease in associations with creatinine-corrected 2,4,6-TCP and PCP concentrations were also achieved. Considering sex difference, the associations of lower birth weight were only found among male neonates, while head circumference was associated with 2,4-DCP and 2,5-DCP only found among female neonates. This study showed significant negative associations between CPs exposure and reduction in neonatal anthropometric measures. The biological mechanisms concerning CPs exposure on fetal growth deserved further investigations.

1. Introduction

Chlorophenols (CPs), known as ubiquitous environmental contaminants, have been extensively used as raw materials or intermediates for agricultural, industrial and domestic purposes, such as in manufacturing pesticides, insecticides, pharmaceuticals, leather and wood preservatives, and fungicides (Olaniran and Igbinosa, 2011). Additionally, the chlorine bleaching of wood pulp and the chlorination disinfection of domestic water supplies may produce CPs (Jensen, 1996). Some of CPs, such as 2,4-dichlorophenol (2,4-DCP), 2,4,6-trichlorophenol (2,4,6-TCP) and pentachlorophenol (PCP) have been regulated as priority pollutants by the US Environmental Protection Agency (EPA), European Commission (EC) Environmental Directive (2455/2001/EC) and China due to their high toxicity to aquatic life, persistence and bioaccumulation potential (EC, 2001; USEPA, 1991; Xing et al., 2012; Zhou et al., 1990). However, CPs as well as their precursors are still widely used as pesticides (Olaniran and Igbinosa, 2011). In China, especially for PCP, the annual national output of PCP was 3010 t in 2003 (Tan and Zhang, 2008). As a result of substantial applications, environmental monitoring investigations have confirmed the presence of CPs in surface and ground waters, bottom sediments, atmospheric air and soils (Czaplicka, 2004; Gao et al., 2008; Sim

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* Corresponding author.
E-mail address: chwu@shmu.edu.cn (C. Wu).

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et al., 2009). Meanwhile, CPs can be detected in various types of human biological samples, including maternal urine during pregnancy, cord blood, breast milk and amniotic fluid in many countries (Bradman et al., 2003; Forde et al., 2015; Hong et al., 2005; Kim et al., 2014; Philippat et al., 2013; Sandau et al., 2002), which suggested prenatal CPs exposures in utero and potential adverse effects on fetal growth.

Exposure to CPs and their derivatives may cause adverse health outcomes containing histopathological alterations, genotoxicity, mutagenicity, and carcinogenicity in humans and animals, which were reviewed by Igbinosa et al. (2013). For PCP, strong associations were presented between occupational PCP exposure and cancer risk in multiple studies (Cooper and Jones, 2008; Zheng et al., 2013). Recently, exposure to CPs has attracted growing public concern because certain CPs have been suspected to disrupt the endocrine function and thus affect reproduction and development in human. For example, paternal PCP exposure was associated with spontaneous abortion in humans (Chen et al., 2013), and obesity (Wei et al., 2014; Buser et al., 2014) and pubertal development in adolescent girls (Buttke et al., 2012; Wolff et al., 2010) were found in associations with exposure to 2.5-DCP due to its potential endocrine-disrupting activity. Moreover, exposure to high levels (>3.58 μg/g) of urinary 2,4,6-TCP may increase the risk of attention deficit hyperactivity disorder among US school-aged children (Xu et al., 2011).

Generally, infants exposed in utero and during critical periods of the early life are especially susceptible due to their rapid growth, cell differentiation, immature metabolic pathways and development of vital organ systems (Eskenazi et al., 1999). Previous studies have suggested occupational exposure to CPs during pregnancy was associated with adverse health effects. Dimich-Ward et al. (1996) found that paternal exposure to chlorophenates in the sawmill industry was associated with the certain developing congenital anomalies of their offspring. Likewise, Seidler et al. (1999) reported that maternal occupational exposure to CPs might be associated with small for gestational age infants at birth. However, few studies have focused on associations between prenatal multiple CPs exposure in the general pregnant population and adverse birth outcomes including weight, length and head circumference at birth. Wolff et al. (2008) observed that maternal higher exposure to 2,5-DCP, not 2,4-DCP during pregnancy predicted lower birth weight and length in boys. A birth cohort study conducted by Philippat et al. (2012) indicated the negative associations between maternal urinary 2,4-DCP and 2,5-DCP concentrations and birth weight. But the association of maternal DCP exposure and neonatal birth size is still controversial. Another study with a larger sample size by Philippat et al. (2014) found no significant association between concentrations of DCPs and birth weight. Compared to DCPs, relatively few data are available concerning the effects of prenatal exposures to trichlorophenol (i.e. 2,4,5-TCP and 2,4,6-TCP) on fetal growth parameters in humans. In experimental animal studies, exposure to 2,4,6-TCP during pregnancy was related to reproductive toxicity as reduction in litter weights at birth on rat (Blackburn et al., 1986) and developmental toxicity on aquatic organisms (Yin et al., 2003). Similarly, a significantly reduced birth weight and length between PCP exposed and non-exposed pregnant women has been examined (Karmaus and Wolf, 1995). These limited findings raised concern over the potential health effects of multiple CPs exposure on the fetus growth. Generally, 2,4-DCP, 2,5-DCP, 2,4,5-TCP and 2,4,6-TCP, are rapidly metabolized and excreted in urine with elimination half-lives less than 24 h (Czaplicka, 2004) and approximately 86% of the total PCP body burden is eliminated in urine with a 20-day half-life in the human body (Zheng et al., 2012). Urine is considered to be the most appropriate matrix for biomonitoring chemicals with shorter half-life (Dekant and Völkel, 2008) and urinary concentrations can be frequently monitored to reflect the exposure assessment. Therefore, the aim of the present study was to evaluate prenatal exposure to CPs by measuring maternal urinary CP concentrations during pregnancy and examine their potential associations with birth outcomes in a birth cohort from an agricultural region of Jiangsu Province, China.

2. Methods and materials

2.1. Study subjects

From June 2009 through January 2010, healthy pregnant women who delivered their babies in a Maternity Hospital in Sheyang County of Jiangsu Province, China, were enrolled into the present study. Detailed descriptions for the study were published in our previous reports (Lv et al., 2016; Qi et al., 2012). Briefly, eligible subjects included in the present study were those with complete questionnaire data, valid prenatal monitoring data on CPs, and birth outcome records. We excluded 49 pregnant women because of stillbirth (1), congenital anomalies (9), multiple births (9) as well as cases with an incomplete data for the requirements of the study (30). Therefore, the final participants consisted of a total of 1100 pairs healthy mothers and their singleton newborns in the birth cohort. All participants had written informed consent and were willing to donate their urine before delivery. This study protocol was approved by the Ethics Committees of School of Public Health, Fudan University, China.

2.2. Urinary CP concentrations analysis

Maternal spot urine was collected on parturition day, prior to delivery and then transferred to the high-density polypropylene centrifuge tubes (Corning Incorporated, USA). All samples were immediately stored at −20 °C, then shipped in a frozen state to the laboratory and kept frozen at −80 °C until analysis (Qi et al., 2012). Urinary creatinine was measured to correct for variability in urinary dilution among spot samples. Five CP compounds were measured in urine samples by large-volume-injection gas chromatography-tandem mass spectrometry (LVI-GC-MS-MS) (Lu et al., 2015). Briefly, the urine samples were prepared by hydrochloric acid hydrolysis, liquid-liquid extraction, solid-phase extraction clean and derivatization. The average recoveries of all CPs were nearly 100% and the limits of detection (LOD) for CPs were 0.01 μg/L.

2.3. Measurement of birth outcomes

Information on newborn birth outcomes, including gestational age (weeks), birth weight (g), birth length (cm) and head circumference (cm) was obtained from maternity hospital records. Namely, weight, length and head circumference were measured immediately after delivery by the midwife in the delivery room. Birth weight was measured using a digital scale and rounded to 0.05 kg. Birth length were measured using measuring tape and rounded to the nearest 0.1 cm. The ponderal index (PI) known to be a good indicator used to quantify asymmetric fetal growth restriction (Landmann et al., 2006) and reflect adiposity in infants, was calculated as the ratio of birth weight in grams to length in centimeters cubed. Especially, a low PI can reflect post-maturity as fat mass is mobilized after the placenta becomes inadequate to sustain the accumulation of fat. Low birth weight was defined as <2500 g.