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Maternal urinary carbofuranphenol levels before delivery and birth outcomes in Sheyang Birth Cohort

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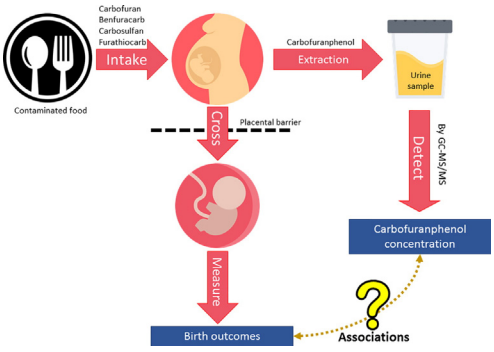
HIGHLIGHTS

- A prospective, relatively large study with efficient exposure measurement technology.
- Carbofuranphenol was detected in all maternal urine samples.
- Generalize linear models were performed to explore associations between carbofuranphenol level and birth outcomes.
- Maternal urinary carbofuranphenol was associated with head circumference and ponderal index in male infants.

GRAPHICAL ABSTRACT



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ABSTRACT

Exposure to carbamates has been linked with adverse health effects on developmental period. This study aimed to monitor exposure to carbofuranphenol of pregnant women from Sheyang Birth Cohort and investigate associations between prenatal exposure to carbofuranphenol and birth outcomes. During June 2009 to January 2010, 1100 pregnant women living in Sheyang County participated in our study and donated urine sample. Urinary carbofuranphenol concentration was measured by gas chromatography–tandem mass spectrometry. Associations between urinary carbofuranphenol levels and infant birth outcomes were assessed by generalized linear models. Urinary carbofuranphenol concentrations varied from 0.01 to 395.40 μg/L (0.01–303.93 μg/g for creatinine adjusted), the geometric mean, median and inter quartile range are 0.81 μg/L (1.28 μg/g cr), 0.80 μg/L (1.23 μg/g cr) and 0.27–2.20 μg/L (0.47–3.11 μg/g cr), respectively. No statistically significant association between maternal urinary carbofuranphenol levels and birth outcomes was found in total infants and female infants. In male neonates, carbofuranphenol level was significantly associated with head circumference ($b = -0.226$; 95% confidence interval: −0.411, −0.041; P = 0.01) and ponderal index ($b = 0.043$, 95% CI: 0.004, 0.083; P = 0.03). These findings suggested that the pregnant women were generally exposed to carbofuranphenol and prenatal exposure to carbofuranphenol might have adverse effects on fetal development.

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1. Introduction

Carbofuran and its derived carbamate pesticides (i.e. benfuracarb, carbosulfan and furathiocarb) (Hill et al., 1995) are widely used in agriculture and pest control. Considering these pesticides persisting in environment may have adverse effects on ecological environment and human health, US and Europe issued acts to restrict the application of carbofuran, benfuracarb and carbosulfan (Environmental Protection Agency, 2006; European Commission, 2006a, 2006b, 2006c). But carbamates are still widely used in agriculture in other countries around the world (Center of Disease Control and Prevention, 2017a). In China, carbofuran was also restricted to use on vegetables, fruits, tea and Chinese herbs, but carbofuran, benfuracarb and carbosulfan are still legally applied for cotton and cereal production(China Pesticide Information Network, 2017), and annual carbofuran application in 2015 was about 12,438 tons (Xinjiang Agriculture Web, 2017). In China, environmental monitoring has confirmed the presence of carbofuran and its derived products in groundwater, soils and agriculture products (Fang et al., 2015; Geng et al., 2017; Xu et al., 2016; Zhang et al., 2016). For general population, body burden of carbofuran is mainly sourced from the consumption of contaminated food (Forde et al., 2015). The potential adverse health effects of low-level exposure to carbamates have attracted attention.

Experiments on adult rats, rat pups and dogs have shown that carbofuran can cross-placental barrier and produce nonspecific developmental effects, such as reducing weight gain, reducing pup survival and having testicular toxicity (Mishra et al., 2012; Pant et al., 1995; Pant et al., 1997; WHO, 2004). Other studies on rodents showed that exposure to carbofuran causes hormones unbalance, that may also affect fetal development in utero (Baligar and Kaliwal, 2002; Goad et al., 2004). Because fetus' metabolic mechanism and physical barriers are immature, carbofuran exposure during prenatal and postnatal period may cause long-term health effects on physical and neural development and endocrine homeostasis (Segerstrom and Miller, 2004).

In recent years, a few of epidemiological studies reported that exposure to carbofuran pesticides may affect birth outcomes. A study on 150 mother-infant pairs in New Jersey, USA reported that carbofuran concentration in cord blood was negatively associated with head circumference of infants (Barr et al., 2010). Another study on mother-infant pairs in Fuyang, China showed that prenatal exposure to multiple pesticides including carbofuran may lead to low birth weight and impaired neuro maturation (Sturza et al., 2016; Wickerham et al., 2012).

Carbofuran and its derived products are metabolized into carbofuranphenol (2, 3-dihydro-2, 2-dimethyl-7-hydroxybenzofuran) and 3-ketocarbofuran that eliminated in urine (Ferguson et al., 1984). In animal models, carbofuran was eliminated rapidly ($t_{1/2} = 29 \pm 5$ min) in rats (Ferguson et al., 1984), elimination after 6, 12, 24, 48 h were 21.4%, 37.8%, 72.2%, 87.7%, respectively (Dorough, 1968). Since carbofuranphenol is a main degradation metabolite of carbamates, urinary carbofuranphenol level was used as a biomarker to assess exposure dose in epidemiological studies (Castorina et al., 2010; Center of Disease Control and Prevention, 2017b; Forde et al., 2015).

In the present study, we aimed to quantify the body burden of carbofuranphenol among the pregnant women from Sheyang County and evaluate the association between prenatal carbofuranphenol exposure and birth outcomes.

2. Materials and methods

2.1. Study population

This study was based on the Sheyang Birth Cohort (SBC), a prospective cohort focusing on environmental pollutant exposures and growth development during prenatal and postnatal period (Qi et al., 2012). Sheyang County is located in East China (N 33°46, E 120°15′) and has a Yellow Sea coastline of 103 km, it's the biggest county in Jiangsu Province with a population of one million. The flat terrain of alluvial plain and subtropical monsoon climate are suitable for agricultural production. Rice and cotton from Sheyang can be bought all over China, planting industry is one of economic pillars of Sheyang. Carbofuran is one of the most widely used pesticides in the county (Qin et al., 2007).

During June 2009 to January 2010, a total of 1303 healthy pregnant women resided in Sheyang County over one year volunteered to participate in Sheyang Birth Cohort study and donated their urine samples at the Sheyang Maternity Hospital. (Guo et al., 2016; Lv et al., 2016; Qi et al., 2012).

In current study, 203 mother-infant pairs were excluded because of stillbirth (1 pair), congenital anomalies (9 pairs), multiparity (9 pairs), incomplete data (30 pairs) or lack of urine sample (154 pairs). Finally, a total of 1100 pairs of healthy mothers and their singleton neonates were included.

The study protocol was approved by the Ethics Committee of the School of Public Health, Fudan University.

2.2. Urine sample collection and analysis

The urine samples were collected on the day of delivery. Urine sample collected in polypropylene centrifuge tubes and stored at −20 °C immediately, and shipped in a frozen state to the laboratory and kept frozen at −80 °C until analysis (Qi et al., 2012). A large-volume-injection gas chromatography-tandem mass spectrometry (GC–MS/MS) assay was developed for urinary carbofuranphenol quantification (Lu et al., 2015). Briefly, the urine samples were prepared through hydrochloric acid hydrolysis, liquid-liquid extraction, solid-phase extraction clean and derivatization. The average recovery of carbofuranphenol was nearly 100% and the limit of detection (LOD) for carbofuranphenol was 0.01 μg/L.

Creatinine concentrations were measured using ELx800 Universal Microplate Reader (BIO-TEK, USA).

2.3. Measurement of birth outcomes

Information on birth outcomes, including gestational age (weeks), birth weight (g), birth length (cm) and head circumference (cm) were obtained from maternity hospital records. Namely, weight, length and head circumference were measured immediately after delivery by the midwife. 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. Ponderal index (PI), known to be a good indicator used to quantify asymmetric fetal growth restriction and reflect adiposity in infants was calculated as (birth weight in kilograms) / (length in meters)^3 (Fayyaz, 2005).

2.4. Statistical analysis

Student's *t*-test and Fisher's exact test were performed to examine difference between the included and excluded subjects. Differences of carbofuranphenol levels among subgroups were examined by Kolmogorov-Smirnov test and one-way analysis of variance (ANOVA).

Generalized linear model (GLM) was used to investigate the associations between urinary carbofuranphenol level and birth outcomes, adjusting for covariates. We used creatinine-corrected concentration of carbofuranphenol to normalize urine dilution variation. Log-transformation was used to correct skewed distribution. In order to determine appropriate covariates, we identified factors associated with fetal growth according to previous literatures (Barr et al., 2010; Guo et al., 2016), including gestational duration (week), maternal age (year), pre-pregnant body mass index (BMI, kg/m^2), gestational weight gain (kg), education level (middle school or lower, high school or higher), parity (0 or more), pregnancy smoking (active and/or passive smoking or not), family annual income (≤30,000 RMB, >30,000 RMB) and neonatal sex (male or female). Furthermore, delivery mode