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Association of *in utero* exposure to organochlorine pesticides with thyroid hormone levels in cord blood of newborns☆

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ABSTRACT

Organochlorine pesticides (OCPs) had been widely used in agriculture and disease prevention from the 1940s–1960s. Currently, OCPs are raising global concerns due to their associated prevalent contamination and adverse health effects, such as endocrine disruption. Several epidemiological studies have explored the underlying association of OCPs on thyroid hormone (TH) status in adults and newborns, but the results of studies performed on newborns are often inconclusive. This exploratory study was conducted with the purpose of assessing the potential association of the prenatal exposure to OCPs with the concentrations of TH in the cord blood of newborns from China. Cord blood and information on demographic characteristics were collected from 115 newborns between November 2013 and June 2014. The exposure levels of 17 OCPs were measured with a gas chromatography/mass spectrometry, and TH levels including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were detected using electrochemiluminescence immunoassay methods. After adjusting for confounding factors (the age of pregnant mothers, education level, monthly household income, parity, and sex of the newborns), we found marginally significant inverse associations of cord plasma measurements of ∑hexachlorcyclohexanes (∑HCHs), 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (ρ,ρ′-DDE) and methoxychlor with FT4 levels, but not with FT3 and TSH levels. Moreover, higher cord plasma levels of aldrin, dieldrin, ∑dichlorodiphenyltrichloroethanes (∑DDTs), ∑Drins, and ∑OCPs were found to be related to the increase in cord plasma TSH levels after the adjustment for confounders. The results of this exploratory study indicate that *in utero* exposure to certain OCPs may affect TH status in newborns, and therefore, pose potential effects on early human development. Further research, with larger sample sizes, should be conducted to confirm these findings.

1. Introduction

Organochlorine pesticides (OCPs) have been extensively applied in the agricultural industry and for controlling mosquito populations worldwide since the 1940s. As a developing country with a large agricultural economy, China had been one of the largest producers and consumers of OCPs globally, from the 1950s to 1983 (Li et al., 2014). However, concerns about the potential health threats of OCPs contamination had been growing as more and more evidence has demonstrated the adverse effects of OCPs. The properties of OCPs include a long half-life, high lipophilicity,

Abbreviations: OCPs, organochlorine pesticides; TH, thyroid hormone; T3, triiodothyronine; FT3, free triiodothyronine; TT3, total triiodothyronine; T4, thyroxine; FT4, free thyroxine; TT4, total thyroxine; TSH, thyroid-stimulating hormone; HCH, hexachlorcyclohexane; ρ,ρ′-DDT, 1,1,1-trichloro-2,2-di(4-chlorophenyl) ethane; ρ,ρ′-DDE, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene; HCB, hexachlorobenzene.

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environmental persistence, and long-range atmospheric transport, which facilitate their ubiquitous distribution in the environment or the bioaccumulation and biomagnification in living organisms via the food chain (Clarkson, 1995; Shen et al., 2005; Sheng et al., 2013). Although most kinds of OCPs had been prohibited or restricted since the 1970s, they are still frequently found all over the world. Relevant studies have reported that OCPs could be detected in various environment media such as soil (Tao et al., 2005), surface water (Huang et al., 2013), air (Kirchner et al., 2016), sediment (Yang et al., 2015), and foods (Zhou et al., 2012). Furthermore, OCPs were even found in biological samples, such as blood (Wang et al., 2013), adipose tissue (Bräuner et al., 2012b), and human milk (Rojas-Squella et al., 2013).

Growing evidence has also demonstrated the adverse health effects of OCP exposures, including, immunotoxicity (Corsini et al., 2008; Mokarizadeh et al., 2015; Tryphonas et al., 2003), reproductive toxicity (Bretveld et al., 2006; Singh et al., 2008), nervous system injury (Ren et al., 2011; Sharma et al., 2010), adverse birth outcome (Dewan et al., 2013; Pathak et al., 2009), and development of cancer or tumors (Arrebola et al., 2015; Bräuner et al., 2012a; Xu et al., 2010). Particularly, as typical environmental endocrine disruptors, OCPs were speculated to disturb the homeostasis and function of the thyroid gland. The associations of OCP exposure with thyroid hormones (TH) levels were found in animal experiments and human epidemiological studies (Maervoet et al., 2007; Meeker et al., 2007; Sørmo et al., 2005; Scollon et al., 2004; Tebourbi et al., 2010). A variety of possible mechanisms had been hypothesized for the effects of OCPs on TH levels. Of these mechanisms, OCPs were suggested to interfere with hormone receptors, competitively bind to TH transport proteins, and alter the release or elimination of triiodothyronine (T3) and thyroxine (T4) (Lopez-Espinosa et al., 2010; Mnif et al., 2011). It is well established that THs are essential for metabolic regulation and maintenance of organ functions, especially, for normal brain development during early human life (Langer, 2010). It has been speculated that the developmental neurotoxicity of some OCPs may partly result from OCPs-mediated thyroid dysfunction (Chevrier et al., 2008). During the critical brain development period of neuroblast proliferation, the fetus and infants show greater susceptibility to the toxic effects of environmental endocrine disruptors than adults (Mnif et al., 2011). Therefore, subtle alterations of TH levels during the early fetal period may lead to irreversible impairment of neurocognitive development in infants and children (Lopez-Espinosa et al., 2010). In addition, OCPs could readily pass through the placenta, posing a potential risk to the developing fetus (Sala et al., 2001; Waliszewski et al., 2000). For these reasons, a few epidemiologic studies have demonstrated the adverse effects of *in utero* exposure to OCPs on TH levels in newborns (Asawasinsopon et al., 2006; Kim et al., 2015; Takser et al., 2005). However, to date, relevant studies on the relationships of a variety of OCPs with TH levels among newborns were limited, with inconclusive results.

In the present exploratory study, we aimed to assess the relationship between prenatal exposure to OCPs and TH levels in newborns from a birth cohort study in China, with the hope to elucidate the potential mechanism of *in utero* OCPs exposure on health effects, especially in regards to the neurodevelopment of infants.

2. Materials and methods

2.1. Study population and sample collection

Pregnant women (n = 120) participating in this study were enrolled during their visits to hospitals in Henan, which were randomly selected from a birth cohort study of China performed between November 2013 and June 2014. The objective of this prospective cohort study of 1000 participants was to explore the relationships of prenatal exposure to mutagenic pollutants with congenital disabilities and to develop biomonitoring technologies for environmental pollutants. Women who met our inclusion criteria were recruited in our study as previously described. All the pregnant women were asked to finish a self-reported questionnaire with the help of a skilled interviewer. The questionnaire was administered to gather data on demographics, lifestyle, and reproductive characteristics (e.g., maternal age, maternal education, monthly household income, smoking habits, parity, and history of disease). In addition, information on sex and anthropometric measurements (i.e., birth weight, birth length) of newborns were obtained from the hospital clinical records. None of the participants consumed alcoholic beverage during pregnancy. Because of the availability of cord blood volume and missing information on demographics, only 115 women in total were included in the current analysis. Approximately 10 mL of cord blood was gathered during labor and delivery. After centrifugation, all plasma samples were collected and frozen at −80 °C before further laboratory analysis. A detailed description of the study was provided to all the participants prior to their signature on the informed consent form. The study was reviewed and approved by the Ethics Committee of the National Institute for Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention.

2.2. Laboratory analysis

The cord plasma samples were analyzed for 17 OCPs from the Environmental Protection Agency (EPA) Appendix IX, including, hexachlorcyclohexanes (α-HCH, β-HCH, γ-HCH, and δ-HCH), 1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane (ρ,ρ'-DDT) and its metabolites (ρ,ρ′-DDE, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene; ρ,ρ′-DDD, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethane), aldrin, dieldrin, endrin, endrin aldehyde, heptachlor, heptachlor epoxide, endosulfan I, endosulfan II, endosulfan sulfate, and methoxychlor, with the concentrations of 2000 μg/mL each component in hexane: toluene (1:1) (Sigma-Aldrich, St. Louis, MO, USA). The isotope-labeled internal standard (hexachlorobenzene-$^{13}C_6$, HCB-$^{13}C_6$), hexane, as well as dichloromethane (DCM) (pesticide grade) were bought from Sigma, in which the isotopic purity of 10 mg $^{13}C_6$-labelled HCB was 99 atom % ^{13}C. Methanol was obtained from Merck KgaA (Darmstadt, Germany).

Laboratory analysis of OCPs in the plasma samples and quality control procedures were performed according to a previously described method elsewhere (Luo et al., 2016). Briefly, plasma samples (0.5 mL) spiked with $^{13}C_6$-labelled HCB were first fortified with deionized water and urea for protein denaturation. Then solid phase extraction of OCPs from plasma samples were conducted on Oasis® HLB extraction cartridges (3 cm^3/60 mg), in which the HLB cartridges were pre-washed and conditioned with DCM, methanol, and deionized water successively. The extraction cartridges, loaded with plasma samples, were rinsed with deionized water. Subsequently, 5 mL of elution mixture (DCM and hexane 1:9; v/v) was applied to elute the analytes of interest. After removing HLB cartridges, combined eluents were concentrated and dissolved in 100 μL of hexane for instrumental measurements. An Agilent 6890N gas chromatography coupled with 5975B mass spectrometry system (Agilent Technologies, Palo Alto, CA, USA) was used for the identification and quantification of OCPs as described previously (Luo et al., 2016). In addition, a DB-5 ms capillary column (30 m × 0.25 mm × 0.25 μm) was applied for the separation of various OCPs. The mass spectrometry was performed under the selective ion monitoring mode using molecular ions of target compounds. In the process of quality control, an internal standard