Science of the Total Environment 610–611 (2018) 191–199

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Prenatal exposure to dioxin-like compounds is associated with decreased cord blood IgE and increased risk of wheezing in children aged up to 7 years: The Hokkaido study☆

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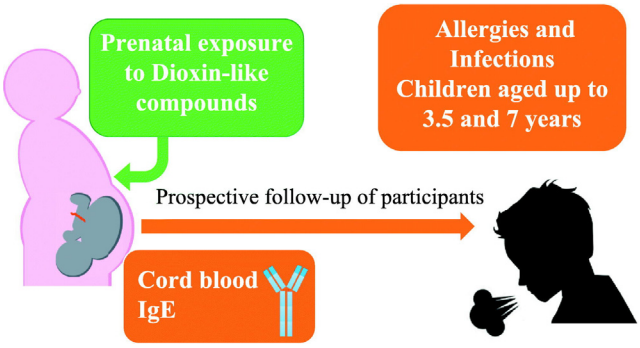
HIGHLIGHTS

- In utero exposure to dioxin-like compounds (DLCs) affects infant immune development.
- Maternal blood DLC levels were lower than other areas in Japan, the USA, and Europe.
- Maternal DLC negatively associated with cord blood IgE & wheezing in boys at 3.5 yrs.
- Maternal DLC positively associated with wheezing in boys and girls at 7 yrs.
- Allergic symptoms are more obvious in older children due to matured immune function.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 12 May 2017
Received in revised form 5 July 2017
Accepted 28 July 2017
Available online xxxx

Editors: D. Barcelo and Jay Gan

Keywords:
Dioxin-like compounds
Prenatal exposure
IgE
Allergy
Infection
Children of school age

ABSTRACT

Introduction: In utero exposure to dioxin-like compounds (DLCs) may cause imbalance of immune development in early infancy. However, there are few epidemiological studies into the effects of in utero exposure to DLCs on allergies and infections during childhood. This study evaluates associations between concentrations of maternal DLCs and cord blood immunoglobulin (Ig) E, as well as allergies and infections during childhood.
Method: We recruited 514 pregnant women in a maternity hospital in Sapporo, Japan, and measured concentrations of DLCs in 426 maternal blood samples using high-resolution gas chromatography/high-resolution mass spectrometry. We examined the relationship between concentrations of maternal DLCs and cord blood IgE at birth ($n = 239$), as well as for allergies and infections in children at 3.5 ($n = 327$) and 7 ($n = 264$) years, using regression analysis adjusted for confounding variables.
Results: We found a positive association between maternal DLC concentrations and frequency of wheezing in children aged up to 7 years [odds ratio (OR); 7.81 (95% confidence interval (CI), 1.42 to 42.9)]. At 3.5 years, boys showed inverse associations between maternal DLC concentrations and cord blood IgE [partial regression coefficient; −0.87 (95% CI), −1.68 to −0.06], and frequency of wheezing [OR; 0.03 (95% CI), 0.00 to 0.94] but girls did not.
Discussion: As one reason for the significant association observed at 7 but absent at 3.5 years, we suggest that

Abbreviations: AHR, aromatic hydrocarbon receptor; CI, confidence interval; DLC, dioxin-like compound; Ig, immunoglobulin; HRGC/HRMS, high-resolution gas chromatography/high-resolution mass spectrometry; β, partial regression coefficient; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PCB, polychlorinated biphenyls; RSV, respiratory syncytial virus; TEF, toxic equivalent factor; TEQ, toxic equivalent.

☆ Declaration of competing financial interests: the authors declare they have no actual or potential competing financial interests.

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http://dx.doi.org/10.1016/j.scitotenv.2017.07.248

allergic symptoms are more obvious in older children due to matured immune function.
Conclusion: The findings suggest that prenatal exposure to DLCs may modify offspring immune responses and result in increased risk of allergy among children of school age.

1. Introduction

The general population experiences widespread exposure to persistent organic pollutants, including dioxin-like compounds (DLCs) from environmental sources and daily food intake (Todaka et al., 2008). Seventeen polychlorinated dibenzo-*p*-dioxins/polychlorinated dibenzofurans (PCDDs/PCDFs) and 12 polychlorinated biphenyls (PCBs) have been categorized as DLCs (Van den Berg et al., 2006). In utero exposure to DLCs can cause various toxicities, including carcinogenicity, teratogenicity; endocrine, immune, and reproductive disruption; and neurobehavioral effects (WHO, 2012). DLCs are aromatic hydrocarbon receptor (AHR) agonists that disrupt normal fetal development by binding to AHRs (Van den Berg et al., 2006).

Animal studies have demonstrated that fetal 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure inhibits cellular differentiation and maturation, particularly of T lymphocytes; causes thymic atrophy; and leads to immunosuppression in offspring (Yoshizawa et al., 2007). In humans, a systematic review by Gascon et al. (2013) included several studies reporting higher risk of respiratory infections, including acute otitis media, among infants (Chao et al., 1997; Dallaire et al., 2004; Glynn et al., 2008; Miyashita et al., 2011; Stolevik et al., 2011) in relation to in utero exposure to PCBs and/or dioxins. In the Rotterdam study of the Netherlands cohort, dioxins in breast milk were significantly associated with a higher prevalence of infections as well as a lower prevalence of shortness of breath with asthma at 42 months. In addition, these indicators were related to a reduction in antibody responses to vaccinations and an increased number of T-lymphocytes at 42 months (Weisglas-Kuperus et al., 2000). In Japan, increased concentrations of DLCs were significantly associated with increased lymphocyte subset ratio in offspring (Nagayama et al., 2007). Most of the current knowledge about in utero exposure to DLCs relates to reduced immune response, and higher incidences of infectious symptoms in early infancy have been relatively consistent.

However, human studies focusing on possible long-term effects of in utero exposure to DLCs on outcomes for allergic and infectious symptoms among school age children and young adults are scarce. In the Rotterdam study, higher PCB levels, but not dioxins in breast milk, were associated with less shortness of breath with wheezing at 7 years (Weisglas-Kuperus et al., 2004). In the Amsterdam study of the Netherlands cohort, a decrease in allergies at 8 years (ten Tusscher et al., 2003) and decreased lung function among offspring aged 7–12 years were associated with an increasing concentration of DLCs in the mother's breast milk (ten Tusscher et al., 2001). On one hand, in a Danish cohort of 965 pregnant women, there was a positive association between maternal concentration of dioxin-like PCBs and offspring risk of using asthma medication during a 20-year follow-up period (Hansen et al., 2014). The same cohort study indicated that in utero exposure to dioxin-like PCBs appeared to be associated with airway obstruction but not allergic sensitization among the 421 offspring at age 20 (Hansen et al., 2016). The findings of such studies on humans regarding the association between in utero exposure to DLCs and allergies or infections during childhood and adolescence have been inconsistent due to the small number of previous studies on long-term effects of DLCs.

Only one cross-sectional study previously reported a positive correlation for a dioxin-like PCB congener: PCB118 in maternal placental tissue and cord blood IgE using the Spearman correlation (Reichrtova et al., 1999). We have previously reported increased incidence of infections, otitis media at 18 months of age, but not allergy, associated with increasing concentration of DLCs in maternal blood (Miyashita et al., 2011). While that study indicated that in utero exposure to DLCs might affect immune function immediately after birth, we did not evaluate immune response at birth. The present study evaluates associations between concentrations of maternal DLCs and cord blood IgE, as well as allergies and infections in children aged up to 3.5 and 7 years.

2. Materials and methods

2.1. Study participants and collection of baseline questionnaire data and medical records at birth

The participants in this study were enrolled in the Hokkaido Study on Environment and Children's Health. A total of 514 pregnant Japanese women were recruited at the Sapporo Toho Hospital in Hokkaido, Japan, from July 2002 to September 2005 (Kishi et al., 2013). Details regarding the study participants and the collection of baseline questionnaires and medical records at birth have been described previously (Kishi et al., 2013). An overview of this study is shown in Fig. 1. Among the 514 women, 10 were excluded due to miscarriage, stillbirth, relocation, or voluntary withdrawal from the study until birth. Medical records were obtained from 504 participants.

2.2. Data collection from follow-up questionnaires at age 3.5 and 7 years

At 3.5 years post-delivery, participants completed another self-administered questionnaire. Of the 443 women to whom the questionnaire was mailed, 345 (77.8%) responded. Thirty-five participants were excluded due to death of the infant, relocation, or voluntary withdrawal for the follow-up period. At 7 years post-delivery, participants completed another self-administered questionnaire, with a response rate of 71.0% (281/396). The follow-up questionnaires included information related to breast-feeding, environmental exposure to tobacco smoke, keeping pets in the home, living environment, daycare attendance, infant vaccination, and previous or current medical history of infant allergies and infectious symptoms aged up to 3.5 and 7 years.

For this study, all participating women provided written informed consent, and the study protocol was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Center for Environmental and Health Sciences.

2.3. Assessment of infant allergies and infections

Outcomes of allergies and infections during childhood were assessed based on mothers' self-administered questionnaire responses concerning children aged 3.5 and 7 years. Food allergy was defined as a positive response to the following question: “Has your child ever had symptoms such as hives, swelling of the lips, emesis, diarrhea, or respiratory distress when they ate food allergens including milk, egg rice gruel, egg-drop, shrimp, or other foods?” Eczema was defined, using a modified part of the Japanese version of the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire (ISAAC Steering Committee, 1998), as a positive response to the following questions: “1) Has your child ever had an itchy rash which was coming and going for at least 6 months? If yes: 2) Has your child ever had an itchy rash at least one time during 12 months? If yes: 3) Has this itchy rash at any time affected any of the following places: the folds of the elbows,