Thyroid disruption at birth due to prenatal exposure to β-hexachlorocyclohexane

Mar Álvarez-Pedrerol a,⁎, Núria Ribas-Fitó a, Maties Torrent b, Daniel Carrizo c, Raquel Garcia-Esteban a, Joan O. Grimalt c, Jordi Sunyer a,d

a Centre for Research in Environmental Epidemiology-IMIM, Barcelona, Spain
b Primary Health Care Center of Maó, Menorca, Spain
c Department of Environmental Chemistry, Institute of Chemical and Environmental Research (IIQAB-CSIC), Barcelona, Spain
d Pompeu Fabra University, Barcelona, Spain

Received 14 September 2007; accepted 5 December 2007
Available online 22 January 2008

Abstract

Objective: Thyroid hormones play an important role in human brain development, and some organochlorine compounds (OCs) act as thyroid disruptors. The objective of the present study was to evaluate the association between prenatal exposure to organochlorine compounds and thyroid function in newborns from a general population birth cohort in Menorca, with an a-priori specific focus on β-HCH.

Methods: Levels of polychlorinated biphenyls (PCB congeners 28, 52, 101, 118, 138, 153 and 180), hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), dichlorodiphenyl dichloroethylene (p′p′-DDE) and dichlorodiphenyl trichloroethane (p′p′-DDT) in cord serum, and thyrotropin (TSH) concentration in plasma three days after birth were measured in 387 newborns from Menorca. The TSH concentration was categorized (high or low), except for 27 children whose TSH levels were quantified.

Results: Levels of β-HCH and PCB-153 were positively related to TSH concentrations (gestational age-adjusted coefficient (p-value): 0.26 (p = 0.006) and 0.31 (p = 0.050), respectively).

Conclusions: β-HCH is potentially a new thyroid disrupting compound, deserving special interest in future studies given its high body burden in humans.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Hexachlorocyclohexane; Thyroid hormones; Organochlorine compounds; Newborns

1. Introduction

Organochlorine compounds (OCs) are highly lipophilic and chemically stable compounds that have been detected recently in human adipose tissue, milk and blood (Suzuki et al., 2005). Exposure to some OCs have been found to be associated with thyroid hormone concentrations in animals (Hallergen and Damerud, 2002; Braathen et al., 2004) and humans (Hagmar, 2003). Given that thyroid hormones play an important role in human brain development and that the foetus can be exposed to these compounds through the placenta (Suzuki et al., 2005), the effects of OCs in human thyroid function have been studied mainly in newborns (Koopman-Esseboom et al., 1994; Longnecker et al., 2000; Sandau et al., 2002; Fiolet et al., 1997; Steuerwald et al., 2000; Takser et al., 2005; Wang et al., 2005).
Asawasinsopon et al., 2006). Most of these studies have evaluated the effects of PCBs and dioxins (Koopman-Esseboom et al., 1994; Longnecker et al., 2000; Sandau et al., 2002; Fiolet et al., 1997; Steuerwald et al., 2000; Wang et al., 2005), but other OCs such as beta-hexachlorocyclohexane (β-HCH) have been rarely studied. We have previously found an effect of β-HCH on TSH levels at birth in a small cohort of newborns from Ribera d’Ebre, Spain (Ribas-Fito et al., 2003). β-HCH is an isomer of the pesticide formulation of HCH, in which the active insecticidal ingredient is γ-HCH (lindane). β-HCH is the isomer most frequently found in human fat, blood and breast milk, due to its longer biological half-life in the body (Willet et al., 1998).

The general population is exposed to HCH through the inhalation of ambient air and the consumption of contaminated food, and several toxic effects of β-HCH have been described in humans (ATSDR, 2005). However, few studies have assessed the effects of β-HCH on thyroid function in newborns or children.

The objective of this study was to assess the effect of prenatal exposure to a range of OCs, particularly β-HCH, on levels of TSH in newborns in a population birth cohort in Menorca, Spain.

2. Methods

2.1. Study population

This study is based on data from a birth cohort from the general population in the Spanish Balearic Island of Menorca, located in the northwest Mediterranean Sea. Children from the Menorca cohort were participants in the Asthma Multicenter Infant Cohort Study (AMICS), a European study assessing factors causing asthma in children (Polk et al., 2004). This cohort recruited all children born between July 1997 and December 1998, with a total of 482 children being enrolled. Of these children, 387 (80%) had OCs and TSH measured in cord blood and plasma samples, respectively. Written consent was obtained from parents and the study was approved by the ethics committee of the Institut Municipal d’Investigació Mèdica, Barcelona.

2.2. TSH measurement

TSH in newborn plasma was obtained from the national early screening programme of hypothyroidism. In this programme TSH is determined 3 days after birth using immunoassay (ELISA) with a detection limit of 10 mU/l (established to detect cases of hypothyroidism). Therefore, those children with TSH above 10 mU/l had TSH concentrations quantified. Prior to September 1997, a detection limit of 0.1 mU/l had been in use, thus an additional 22 samples from children with TSH concentrations below 10 mU/l were also quantified and are included in these analyses.

2.3. Organochlorine compounds

OCs (HCB, β-HCH, p,p’-DDT, p,p’-DDE, and PCB congeners 28, 52, 101, 118, 138, 153 and 180) were analysed in cord serum samples by gas chromatography (GC) with electron capture detection (Hewlett-Packard 6890N GC-ECD) and GC coupled to chemical ionisation negative-ion mass spectrometry (HP 5973 MSD) which has been previously described, as well as detection limits for all OCs (Carrizo et al., 2006).

2.4. Other variables

Information on paternal education, socioeconomic background, maternal disease and obstetric history, parity, gender and fetal exposure to alcohol and cigarette smoking was obtained through questionnaire. Information on gestational age and anthropometric measures at birth was available from clinical records.

2.5. Statistical analysis

TSH concentrations were categorized as high/low concentrations, taking the detection limit (10 mU/l) as a cut-off point. Levels of OCs were measured in each group of TSH. For a small subsample (n = 27) quantified concentration of TSH was available and Adjusted General Additive Models (GAM) models were used to evaluate the linearity of the relationship between TSH concentration and levels of β-HCH. Subsequent linear regression models were run using the OC levels as independent variables, and the TSH concentration as the outcome (n = 27). OCs and TSH had a non-normal distribution and were log transformed before being included in the models. Normality and homoscedasticity of the residuals were checked using Shapiro–Wilk W test and Breusch–Pagan test, respectively. All models were adjusted by gestational age, mother’s age and mother’s smoking habits during pregnancy, as identified from the literature. No other variables (such as sex or mother’s weight) were included in the models since the level of significance in the association with the outcome in the bivariate analysis was above 0.20. Statistical significance was set at a p-value < 0.05. All analyses were conducted with the STATA 8.2 statistical software package.

3. Results

Table 1 describes the OCs concentrations (geometric mean and 95% IC) in each group of TSH (below and above the detection limit), Mann–Whitney test was used to compare the OCs concentrations between each group, however given that there were only 5 children
with TSH concentrations above 10 mU/l and 382 children with TSH below 10 mU/l no statistically significant differences were observed. Nevertheless, concentrations of OCs in the high TSH group were higher than the concentrations in the low TSH group for the majority of OCs, with the largest differences observed for β-HCH.

The relation between TSH concentration and levels of β-HCH ($n = 27$) using a GAM model is shown in Fig. 1. β-HCH seemed to be positively related to TSH with the relation following a linear pattern.

The adjusted relation between TSH concentration and OC levels is shown in Table 2. All OC levels were positively related with TSH concentration, but only the associations with β-HCH and PCB-153 were statistically significant. Residuals from the model for β-HCH showed a normal distribution and a constant variance. However, it is difficult to distinguish the particular effect of each OC on TSH because of their high correlation (correlations between 0.08–0.86, with a correlation of 0.52 between β-HCH and PCB-153). Thus, we repeated the models for each compound adjusting for the other compounds, and we tested for collinearity using variance inflation factors (VIF). Adjustment for the other OCs had essentially no effect on the results, except for PCB-153 whose coefficient decreased and was no longer statistically significant after adjustment for β-HCH (coefficient (SE): 0.18 (0.15)), while β-HCH remained statistically significantly associated with TSH in all models (data not shown). Moreover, all the variance inflation factors were lower than 10, indicating no collinearity between the different compounds. Models were also repeated excluding children with TSH concentrations higher than 10 mU/ml, and the coefficient for β-HCH remained statistically significant (coefficient (SE): 0.21 (0.08), $n = 22$), but not for PCB-153 (data not shown).

### 4. Discussion

In the present study, β-HCH was positively associated with TSH at birth in a general population birth cohort, consistent with our findings from an earlier study conducted in a birth cohort (Ribera d’Ebre cohort) living in an area surrounding an electrochemical plant (Ribas-Fito et al., 2003).

In the current study, only 5 children had TSH concentrations above 10 mU/l and therefore no statistically significant differences in OCs levels were observed with those children with TSH concentrations below the cut-off. In the previous study (Ribas-Fito et al., 2003), TSH was also analysed as a categorical variable taking the detection limit as a cut-off point (TSH = 10 mU/l), and β-HCH levels were found to be significantly higher in children with high TSH concentrations. Moreover, for a small subset of these children ($n = 21$), the quantified concentration of TSH was also available and a positive association between β-HCH and TSH (coefficient (SE): 0.19 (0.08)) was seen when TSH was treated as a continuous variable, which is similar to the present results (Table 2). However, these results were not reported. Furthermore, the children from the current cohort are being followed-up through childhood. In a cross-sectional study of these children at age 4 years ($n = 259$) using serum measures of OCs and thyroid hormones (free thyroxine and total triiodothyronine) and TSH, we found that β-HCH was inversely related with total triiodothyronine levels (Alvarez-Pedrerol et al., electronic publication).

HCH is an insecticide which has been extensively used world-wide since the 1940s, however its commercial use in most regions has been banned or restricted for two or more decades (Breivik et al., 1999). HCH is one of the most commonly detected organochlorine pesticides in environmental samples and several toxic effects of HCH have been described in humans and animals (Steinmetz et al., 1996; Mathur et al., 2002; Zou and Matsumura, 2003) with the nervous system being the main target of acute exposure (Willet et al., 1998; ATSDR, 2005). Although several papers about health effects in children exposed to other organochlorines, such as DDT and PCBs, have been published, there are few papers about the child health consequences of β-HCH exposure (Damgaard et al., 2006; Khanjani and Sim, 2006). Limited information is available on the specific thyroid effects resulting from HCH exposure in children. Asawansipon R, et al. (2006) analysed several OCs, including β-HCH, and studied the association with TH in 39 newborns from Thailand, however β-HCH was not detected in any serum samples. Mazhitova et al. (1998) studied in Kazakhstan the effects of high exposure to some OCs on the thyroid status of 12 schoolchildren. Although the concentrations of β-HCH were extremely high in some of the children, there was no relation seen with TSH or thyroxine levels.

The major limitation of this study is the small number of children with quantified concentrations of TSH. Moreover, no data on thyroxine and triiodothyronine were available. However, the relation between TSH and OCs was previously evaluated in these children at age 4 years, and in newborns from another Spanish cohort, with consistent results.

In conclusion, these findings suggest that prenatal exposure to β-HCH may affect thyroid function in newborns. Consequently, prenatal exposure to these compounds could have an effect on brain development due to thyroid disruption and thus, specific interest should be given to β-HCH to confirm its potential role with regard to thyroid function and to evaluate its general toxicity.

### Acknowledgements

We are indebted to Carlos Mazón, Mrs. Rosa M. Sabaté and Mrs. Maria Victoria Iturriaga for their assistance in contacting the families and administering the questionnaires. We are also

### Table 2

Adjusted association between TSH and OCs (log transformed) in newborns from Menorca cohort ($n = 27$)

<table>
<thead>
<tr>
<th>OCs</th>
<th>Coefficient (SE)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCB (ng/ml)</td>
<td>0.43 (0.49)</td>
<td>0.390</td>
</tr>
<tr>
<td>p,′DDE (ng/ml)</td>
<td>0.29 (0.39)</td>
<td>0.460</td>
</tr>
<tr>
<td>p,″DDT (ng/ml)</td>
<td>0.02 (0.10)</td>
<td>0.831</td>
</tr>
<tr>
<td>β-HCH (ng/ml)</td>
<td>0.26 (0.09)</td>
<td>0.006</td>
</tr>
<tr>
<td>PCB-138 (ng/ml)</td>
<td>0.04 (0.17)</td>
<td>0.805</td>
</tr>
<tr>
<td>PCB-180 (ng/ml)</td>
<td>0.20 (0.12)</td>
<td>0.117</td>
</tr>
<tr>
<td>PCB-153 (ng/ml)</td>
<td>0.31 (0.15)</td>
<td>0.050</td>
</tr>
<tr>
<td>PCB-118 (ng/ml)</td>
<td>0.05 (0.09)</td>
<td>0.566</td>
</tr>
<tr>
<td>PCBs (ng/ml)</td>
<td>0.28 (0.23)</td>
<td>0.231</td>
</tr>
</tbody>
</table>

*Adjusted for gestational age, mother’s age and mother’s smoking habits during pregnancy.*
grateful to all teachers and parents of the children from Ribera d’Ebre County and Menorca for patiently answering our questionnaires.

References


Halleren G, Darnerud PO. Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats: testing interactions and mechanisms for thyroid hormone effects. Toxicology 2002;177:227–43.


