SEXUAL DISTINCTION IN EFFECTS OF PERINATAL EXPOSURE TO ORGANOCHLORINE PESTICIDES, PCBs AND DIOXINS ON IMMUNE RESPONSE AND THYROID HORMONE SYSTEMS IN JAPANESE INFANTS

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Introduction

Our environments including food have been polluted with some organochlorine compounds such as dioxins, polychlorinated biphenyls (PCBs) and pesticides [1, 2]. Japanese people have also been contaminated with these chemicals [3, 4]. Consequently, some pesticides such as hexachlorocyclohexans (HCHs), 1,1,1-trichloro- 2,2-bis-(4-chlorophenyl)-ethane (DDT), dieldrin and heptachlor epoxide (HCE), and PCBs have been determined in Japanese breast milk [5, 6, 7] and their mean or median concentrations on fat weight basis were about 420, 330, 3, 4 and 110 ppb, respectively [6, 7]. Their levels were considered more than 100 to 10,000 times higher than those of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar polychlorinated biphenyls (Co-PCBs), so-called dioxins, in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalent (TEQ) value as a whole [6]. Therefore, we should give due attention to possible health consequences of these organochlorine pesticides and PCBs as well as dioxins in Japanese infants.

We have already reported effects of the perinatal exposure to these compounds on lymphocyte subpopulations [7, 8, 9, 10] and thyroid hormone statuses [11, 12, 13, 14] in the peripheral blood of Japanese infants. In this study, in order to clarify the sexual distinction in their effects on the immune response and thyroid hormone systems, we investigated the lymphocyte subsets and thyroid related chemicals in the blood of Japanese male and female infants in relation to their concentrations of the breast milk.

Materials and Methods

In this study, ninety-three mothers (mean age : 29 years old and the range : 24 ~ 38 years old) volunteered to participate in all. Pregnancy and delivery were completed without overt signs of serious illness or complications. Only babies born at term (37 to 42 weeks of gestation) without congenital anomalies or diseases were included. Breast milk (50 ~ 100 ml), sampled 2 to 4 months after childbirth, was used to determine concentrations of organochlorine pesticides and PCBs by ECD gas chromatographic method [6, 15] and dioxins by high resolution GC/MS method [6].

About 1 year after birth, 5 to 10 ml of peripheral blood samples were individually obtained from 100 infants (57 males and 43 females). These blood samples were employed to measure lymphocyte subsets by indirect immunofluorescence using monoclonal mouse anti-human antibodies against CD3 for mature T cells, CD4 for helper/inducer T cells, CD8 for suppressor/cytotoxic T cells, CD4 and CD8 double positive (CD4+8+) cells, CD16 for natural killer T cells, CD20 for B cells and HLA-DR for activated T cells (Ortho Pharmaceutical Corp., Raritan, NJ and Becton-Dickinson, Mountain View, CA) [16]. The relative population densities of the lymphocyte subsets were also calculated. These blood samples were also used to determine the serum concentrations of T_3, T_4, TSH and TBG by radioimmunoassay methods using commercially available kits [17].

We are studying the relative risks of toxic chemicals to these biological systems, but not their causality. For this purpose and in order to conduct reliable and robust analysis, the concentrations of the organochlorine compounds, the percentages of the lymphocyte subsets, as well as CD4+/CD8+ ratio, and the serum levels of thyroid related chemicals were categorized into two groups ; namely, the measurements which were less than the mean and equal to or over the mean in each year set by 0 and 1, respectively. Then, Fisher's exact test was applied to the resulted fourfold tables and odds ratios were computed from the tables by logistic regression to evaluate the relative risks. Ninety percent confidence intervals (C.I.) of odds ratios were also counted.

Results and Discussion

Concentration of HCH or DDT was about 100 times higher than that of dieldrin or HCE. Contamination levels of chlordane and PCBs were around 4 ng/g and 3 to 5 times less than those of HCH and DDT. In dioxins, their TEQ levels were computed by using 1998 WHO toxic equivalency factor (TEF) values [18] and the mean concentration was about 1 pg-TEQ/g, which was around 180 times lower than those of dieldrin and HCE.

Higher levels of T_3, T_4 and TSH in the serum of Japanese infants were greater than their upper limits of Japanese adults. These hormones play vital roles in an early stage of human life and therefore obviously they are required more in fetuses and sucklings than in adults.

As indicated in Table 1, perinatal exposure to dioxins decreased the CD16 positive lymphocytes in the blood of female infants, but not in the male infants. Dieldrin, DDT and PCBs enhanced the CD16 positive lymphocytes in the blood of male infants, but not in the female infants. Perinatal exposure to dioxins, DDT and chlordane significantly decreased the CD4 CD8 double positive lymphocytes only in the female infants. Dieldrin increased and decreased the CD8 positive lymphocytes in the blood of male infants and in that of female infants, respectively. Dioxins, dieldrin and PCBs significantly enhanced the CD4 positive/CD8 positive lymphocyte ratios only in the female infants. HCE increased the CD3 positive lymphocytes, and HCH and PCBs enhanced the CD20 positive lymphocytes only in the male infants.

Table 1. Effects of perinatal exposure to organochlorine pesticides, PCBs and dioxins on the lymphocyte subsets in the blood of Japanese male and female infants

	Male Infant		Female Infant	
Compound	Odds Ratio	90% C.I.	Odds Ratio	90% C.I.
CD16 Positive Cells				
Dioxins	1.55	0.63 – 3.87	***0.35***	***0.11 - 1.04***
Dieldrin	***2.77***	***1.00 – 8.05***	1.14	0.38 – 3.43
DDT	***3.24***	***1.27 – 8.63***	0.65	0.21 – 1.93
PCBs	***2.33***	***0.90 – 6.18***	0.65	0.21 – 1.93
HLA-DR Positive Cells				
Dieldrin	1.15	0.41 – 3.17	***0.32***	***0.10 – 0.98***
HCE	***0.40***	***0.14 – 1.06***	1.70	0.56 – 5.27
CD4 Positive Cells				
Dioxins	1.35	0.55 – 3.34	***2.50***	***0.85 – 7.65***
Dieldrin	***0.43***	***0.14 – 1.19***	**2.81**	***0.93 – 8.98***
CD4 CD8 Positive Cells				
Dioxins	1.12	0.43 – 2.91	***0.12***	***0.03 – 0.41***
DDT	1.06	0.41 – 2.77	***0.26***	***0.07 – 0.80***
Chlordane	0.84	0.28 – 2.36	***0.14***	***0.04 – 0.46***
CD8 Positive Cells				
Dieldrin	***2.77***	***1.00 – 8.05***	***0.27***	***0.08– 0.82***
CD4 Positive / CD8 Positive Ratio				
Dioxins	0.64	0.25 – 1.56	***3.93***	***1.31 – 12.6***
Dieldrin	0.43	0.14 – 1.19	***7.79***	***2.38 – 29.0***
PCBs	0.69	0.26 – 1.76	***3.12***	***1.05 – 9.87***
CD3 Positive Cells				
HCE	***3.59***	***1.36 – 10.1***	1.44	0.48 – 4.46
CD20 Positive Cells				
HCH	***3.38***	***1.27 – 9.59***	0.40	0.13 – 1.20
DDT	***2.32***	***0.93 – 5.96***	1.18	0.40 – 3.51
PCBs	***2.90***	***1.12 – 7.89***	1.18	0.40 – 3.51

As shown in Table 2, dioxins, chlordane and PCBs significantly decreased the serum levels of T_3 only in the female infants. Dieldrin and HCE enhanced the serum levels of T_4 in the male and female infants, respectively. HCE significantly lowered the serum levels of TSH only in the female infants. HCH and dieldrin increased the serum levels of TBG in the female and male infants,

respectively.

The results mentioned above seem to support the idea of sexual distinction in their effects on the immune response and thyroid hormone systems of Japanese infants. However, this study was done with rather small number of infants. Therefore, further large-scale investigations are required to get more conclusive findings.

Table 2. Effects of perinatal exposure to organochlorine pesticides, PCBs and dioxins on the thyroid hormone system in the serum of Japanese male and female infants

	Male Infant		Female Infant	
Compound	Odds Ratio	90% C.I.	Odds Ratio	90% C.I.
T_3				
Dioxins	0.99	0.41 – 2.41	***0.30***	***0.10 – 0.85***
Chlordane	1.47	0.57 – 3.86	***0.26***	***0.09 – 0.77***
PCBs	1.12	0.44 – 2.82	***0.33***	***0.10 – 0.95***
T_4				
Dieldrin	***3.07***	***1.17 – 8.55***	0.55	0.18 – 1.57
HCE	1.02	0.41 – 2.52	***3.75***	***1.28 – 11.7***
TSH				
HCE	0.86	0.34 – 2.16	***0.30***	***0.10 – 0.90***
TBG				
HCH	1.11	0.44 – 2.83	***3.56***	***1.20 – 11.2***
Dieldrin	***2.75***	***1.05 – 7.64***	1.40	0.47 – 4.16

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