DECREASED CHILDHOOD VACCINE RESPONSE IN CHILDREN EXPOSED TO PCBs FROM MATERNAL SEAFOOD DIET

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Introduction

Persistent organochlorine pollutants are thought to affect immune functions even at current environmental exposure levels (1). For example, *in utero* exposure to heat-degraded polychlorinated biphenyls (PCBs) in Korea resulted in Yu-Cheng disease that was associated with increased frequencies of childhood infections; this observation was linked to reduced immune functions by decreased concentrations of immunoglobulins and lymphocyte subset aberrations in exposed infants (2). More recent data on children exposed to PCBs prevalent in the environment provide additional support for an adverse effect of environmental PCBs on immune functions (3). Experimental animal studies using industrial PCB mixtures suggest that immunotoxicity could constitute the critical adverse effect of these compounds (4). To examine the influence of environmental organochlorines on the human immune function *in vivo*, exposure to these compounds must be linked to clinically meaningful functions of the immune system. Both the Yu-Cheng experience (1,2) and experimental studies (1,4) suggest that perinatal exposure would be of main concern.

A relevant and feasible strategy for a quantitative evaluation of the immune system of infants is to measure antibody responses to immunization with thymus-dependent antigens (5). Antibody production to such antigens is dependent on antigen presentation, T-lymphocyte function, and B-lymphocyte function. Furthermore, antibody production is directly relevant to the efficacy of the immune system in relation to infection (5). The antibody response to routine childhood vaccinations can be measured easily and reproducibly on frozen serum samples using routine laboratory techniques. Especially diphtheria toxoid and tetanus toxoid are highly suitable, because the normal antibody responses to these proteins are well documented.
Dietary exposure to PCBs from contaminated marine food is high in fishing communities such as the Faroe Islands, where pilot whale blubber is part of the traditional diet. While dioxin exposure is not increased, average PCB exposures are up to 10-fold higher than average levels in Northern Europe (6). We therefore examined a Faroese cohort of healthy full term singletons whose mothers had been exposed to PCBs from ingestion of pilot whale blubber. A negative influence of PCB in healthy pregnant women on the ability of their offspring to respond to infant vaccines would suggest an important immune toxic effect of such substances even if such a negative effect, due to the multitude of confounding factors, cannot be expected to result in a strong negative correlation.

Methods

Individuals:

A total of 131 healthy Faroese women giving birth at the National Hospital in Tórshavn, Faroe Islands, to singletons participated in the study as a part of a general evaluation of the influence of maternal ingestion of marine contaminants on neurodevelopment and immune function in their offspring. The women were enrolled consecutively after written informed consent. Only mature infants born after a normal delivery were included. Exposure to marine contamination was evaluated by measuring Hg in maternal hair and PCB congener concentrations in the lipid phase of postnatal day 3-4 mother's milk, in lipids of maternal blood (GW 34) and the blood of the infants at approximately 18 months of age (Table 1). As previously documented (6), an estimate of the total PCB concentration was calculated as 2.0 * (CB-138 + CB-153 + CB-180). Because of the increased PCB exposures, we also calculated the weighted sum of the two main mono-*ortho* substituted CB-118 and

CB-156 using the toxicity equivalency factors (TEFs) (7).

The infants were vaccinated according to the official Danish/Faeroese vaccination program and thus received immunization with diphtheria toxoid, tetanus toxoid, a conjugate *Haemophilus influenzae* type b capsular polysaccharide, acellular pertussis toxoid and inactivated polio at approximately age 3, 5, and 12 months (Table 1). Antibody concentrations against diphtheria toxoid and tetanus toxoid were measured by the Statens Serum Institut, Copenhagen, Denmark, in serum obtained about one month before the third (12 months) vaccination (N: 62) and 5 months after the third vaccination (N: 105). Antibodies were measured by means of standard ELISA methods.

Table 1. Characteristics of 53 boys and 78 girls from the Faroese birth cohort examined at age 18 months.

Variable	
Maternal age in years	29.7 (5.2)
Previous births (none / one / at least two in %)	20.8 / 35.2 / 44.0
Smoking during pregnancy (no / yes in %)	70.4 / 29.6
Alcohol consumption during pregnancy (never / ever in %)	68.0 / 32.0
Gestational age in weeks*	39.5 (1.3)
Birth weight in g*	3690 (487)
Maternal serum PCB concentration in µg/g lipid	1.28 (0.83-2.15)
Milk PCB concentration in µg/g lipid	1.35 (0.84-2.48)
Maternal hair mercury concentration in µg/g	1.68 (0.94-2.77)
Age at 18-month examination in months*	17.7 (1.3)
Child serum PCB concentration in µg/g lipid	1.16 (0.66-2.07)

*Data for continuous variables are given as mean (SD), while pollutant concentrations are given as the geometric mean (interquartile range).
The PCB concentration has been calculated as 2.0 x (CB-138 + CB-153 + CB-180).

Results and Discussion

PCB congener concentrations were strongly related, and the lipid-based concentrations in mother's milk and pregnancy serum were very similar (r Pearson 0.89). These results both correlated well, though not as closely, with PCBs in the serum obtained from the children at 18 months, i.e., after cessation of breast-feeding (Fig 1).

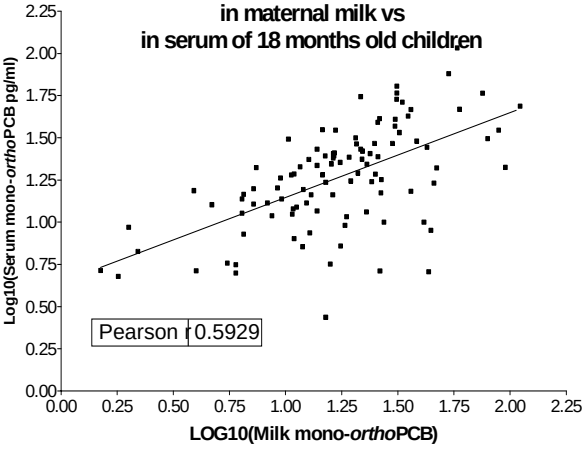

Figure 1

As previously observed (6), the geometric average sum PCB concentration in maternal serum and milk was about 2µg/g lipid, with a maximum about 10-fold higher. All major PCB congeners showed a negative correlation with the concentrations of anti diphtheria toxoid (Table 2). The strongest correlations were obtained with the weighted concentrations of the mono-*ortho* PCBs (Fig 2). The correlation between PCB exposure levels and anti tetanus toxoid concentrations tended to be weaker and not statistically significant.

As expected with a cohort of this limited magnitude the percentage of children with antibody levels below what is assumed to provide long time protection was low. A larger cohort would be needed to allow estimation of the extent to which exposure to PCBs can cause insufficient protection of some vaccinees

In conclusion, these data show that increased perinatal exposure to PCBs may influence antibody production to T-cell dependent antigens in current childhood vaccination programs. This deficit in perinatal immune function could be the result of a dioxin-like adverse effect on thymic development and thereby T-helper cell function.

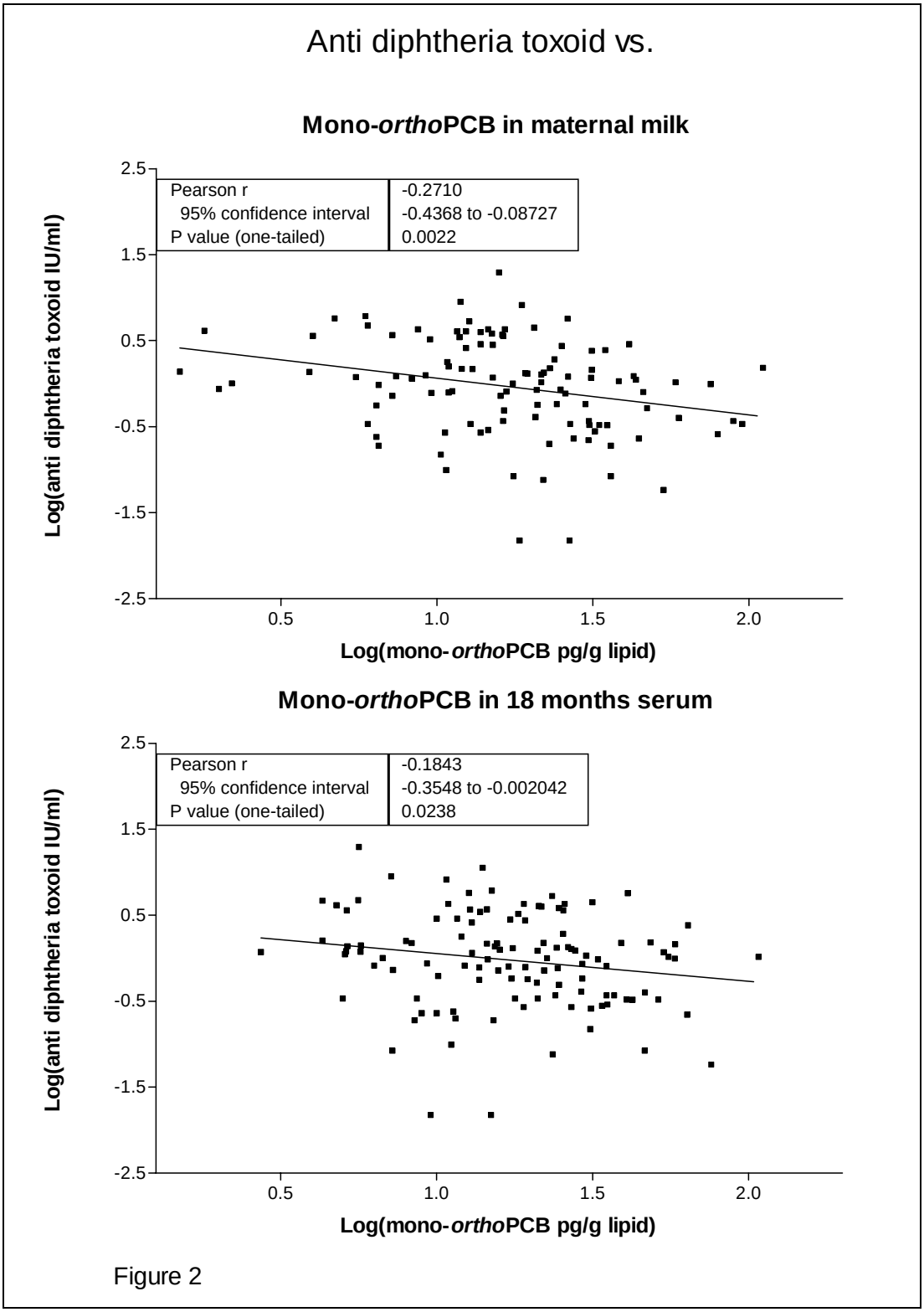
Anti diphtheria toxoid vs.
Mono-orthoPCB in maternal milk
Pearson r -0.2710
95% confidence interval -0.4368 to -0.08727
P value (one-tailed) 0.0022
Log(anti diphtheria toxoid IU/ml)
Log(mono-orthoPCB pg/g lipid)
Mono-orthoPCB in 18 months serum
Pearson r -0.1843
95% confidence interval -0.3548 to -0.002042
P value (one-tailed) 0.0238
Log(anti diphtheria toxoid IU/ml)
Log(mono-orthoPCB pg/g lipid)

Figure 2

Table 2. Association (r Pearson) between biomarkers of perinatal PCB exposure and antibody concentrations after childhood vaccinations against diphtheria and tetanus, as indicated by correlation coefficients between the log transformed variables (p values (one-tailed) in parenthesis).

Exposure parameter	Tetanus	Diphtheria
Maternal serum		
Total PCB	-0.01 (0.479)	-0.16 (0.039)
Weighted mono-*ortho* PCB congeners	-0.04 (0.34)	-0.18 (0.023)
Transitional milk		
Total PCB	-0.07 (0.231)	-0.21 (0.013)
Weighted mono-*ortho* PCB congeners	-0.11 (0.137)	-0.27 (0.002)
Child serum at age 18 months		
Total PCB	-0.17 (0.037)	-0.28 (0.002)
Weighted mono-*ortho* PCB congeners	-0.09 (0.172)	-0.18 (0.024)

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