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Estimated PCDD/F TEQ and total TEQ concentrations in the serum of 7–10 year old Finnish children

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Abstract

Polychlorinated dibenzo-p-dioxins and furans (PCDD/Fs) and polychlorinated biphenyls (PCBs) are persistent organic pollutants that have detrimental health effects. As people are exposed to them mainly through the diet, EU has set maximum food dioxin and PCBs levels. EFSA CONTAM Panel made new risk assessment in 2018 that lowered the tolerable weekly intake (TWI) from 14 pg-TEQ/kg bw/week to 2 pg-TEQ/kg bw/week. Critical effect was decreased semen count at the age of 18-19 years if serum total TEQ at the age of 9 years exceeded the No Observed Adverse Effect Level (NOAEL) of 7 pg/g lipid. However, it is largely unknown to what extent NOAEL is exceed in European boys currently. We thus measured PCBs from small volume of serum in 184 Finnish children 7-10 years of age. To estimate the TEQ levels of children from measured PCB levels, we used our existing human milk PCDD/F and PCB concentrations to create a hierarchical Bayesian regression model that was used to estimate TEQs from measured PCBs. For quality control (QC), three pooled blood samples from 18 – 20 year old males were measured for PCDD/Fs and PCBs, and estimated for TEQs. In QC samples measured and estimated TEQs agreed within 84% – 106%. In our estimate for 7-10 year old children, PCDD/F TEQ exceeded NOAEL only in 0.5% and total TEQ in 2.7% of subjects. Risk management following the decreased TWI proposed by the CONTAM Panel should be carefully considered if total TEQ in children is already largely below the NOAEL.

Highlights:

- Critical Russian study generated a NOAEL of 7 pg total TEQ/g lipid in 9 year old boys
- Nine major PCBs were measured in serum of 184 Finnish children 7–10 years of age
- Bayes model was used to estimate serum total TEQ concentrations with PCBs
- The model predicted that total TEQ was below the NOAEL in 97.3% of children
- Little health benefits are achieved with further reduction in food maximum levels

Keywords

PCDD/Fs, PCBs, impaired semen quality, tolerable weekly intake, European Food Safety Authority (EFSA)

1. Introduction

Polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs) and polychlorinated biphenyls (PCBs) are persistent organic pollutants that accumulate in food chain. People are exposed to them mainly through diet. Fish and seafood are typically the main contributors to dietary PCDD/F and PCB exposure (EFSA, 2012). In addition, the intake of red and white meat, and lean and fatty fish, has been linked to high levels of PCDD/Fs and dioxin-like compounds in maternal blood of European pregnant women (Papadopoulou et al., 2014). In the latest Finnish intake assessment of PCDD/Fs and PCBs conducted 20 years ago the contribution of fish to their intake was around 80% (Kiviranta et al., 2004). In Finland, despite higher intake of PCDD/Fs and PCBs, high consumption of fish has been linked to many beneficial health effects such as lower mortality from all causes and ischaemic heart diseases (Turunen et al., 2008), hypotriglyceridemic and anti-inflammatory effects, improved glucose-insulin metabolism and arterial elasticity (Turunen et al., 2013). A recent review indicates that the benefits of diets providing moderate amounts of fish during pregnancy outweigh potential detrimental effects of environmental contaminants in regards to offspring neurodevelopment (Starling et al., 2015).

On the other hand, both compound groups have various detrimental health effects most of which are mediated through the aryl hydrocarbon receptor (AhR). Toxic equivalency factors (TEFs) have been set based on experimental evidence for 17 PCDD/F congeners and 12 dioxin-like PCB congeners with respect to their potency to induce toxic or biological effects through the AhR. The TEF value of the most toxic congener, TCDD, has been set to 1, and the TEF values of other congeners to 0.00003–1. Multiplication of the measured amount of each congener by its respective TEF value gives the amount that is toxicologically equivalent with TCDD. Summing up the TEF-weighted amounts of all congeners in a mixture gives the approximate amount that is equivalent to TCDD in toxicity (toxic equivalent sum, TEQ) (Van den Berg et al., 2006).

In 2001, the Scientific Committee on Food of the European Commission established a Tolerable Weekly Intake (TWI) of 14 pg TEQ/kg bw/week for PCDD/Fs and PCBs based on detrimental effects on male reproduction, immune system, cognitive recognition and development of endometriosis in experimental animals (SCF, 2001). In November 2018 EFSA published a new report of the Contaminant Panel (CONTAM Panel) "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food" (EFSA, 2018). In the critical Russian study of EFSA risk assessment, increased serum TCDD and PCDD TEQ concentrations at age of 8–9 years were associated with a decreased sperm concentration, total sperm count, and total motile sperm count at the age of 18–19 years (Minguez-Alarcon et al., 2017). From this study, a No Observed Adverse Effect Level (NOAEL) of 7.0 pg PCDD/F TEQ/g lipid in blood sampled at age of 9 years was identified. This was based on the median serum PCDD/F TEQ level in the lowest quartile of the critical Russian study. The CONTAM panel estimated by pharmacokinetic modelling that boys breastfed for 12 months with 800 ml/day of milk containing 5.9 pg TEQ/g lipid followed by weekly intake of 4 pg TEQ/kg bw/week for 8 years will result in the NOAEL serum level of 7.0 pg/g lipid by the age 9 years (EFSA, 2018).

Overall, the CONTAM Panel proposed an adult TWI of 2 pg TEQ/kg bw/week for the sum PCDD/Fs and PCBs (EFSA, 2018). This is a drastic decrease from the previous TWI of 14 pg TEQ/kg bw/week, and according to intake calculations in the EFSA report, a substantial portion of the European population currently exceeds the proposed TWI. From a risk management perspective, this might require lowering the maximum levels (European Commission, 2011) of PCDD/Fs and PCBs especially in fish, which is the most important source of intake in most European countries.

Few data exists on the blood TEQ-levels in European pre-pubertal boys, and it is largely unknown to what extent they currently exceed the NOAEL of 7.0 pg TEQ/g lipid. The required sample volume for PCDD/F and non-ortho-PCB analysis is 50–100 ml of blood, and there are ethical and practical issues that make it virtually impossible to obtain such samples. In Germany, in a pooled

blood sample of 10 year old boys (n=241) in 2002–2003, PCDD/F TEQ was 5.9 pg/g lipid and PCB TEQ 5.6 pg/g lipid (Link et al., 2005). Levels in girls of the same age (pooled sample, n=223) were almost identical. In the Netherlands, individual samples from 14 boys (median age 14.3 years) collected in 2005 had lower median PCDD/F TEQ of 2.3 pg/g lipid (range 0.4–6.1 pg/g lipid) and PCB TEQ of 1.5 pg/g lipid (range 0.04–7.8 pg/g lipid) (Leijs et al., 2008).

The main purpose of this study was to estimate the serum PCDD/F- and total TEQ (sum of PCDD/F TEQ and PCB-TEQ) levels among 7–10 year old Finnish boys in two cohorts, and compare those to the NOAEL of 7.0 pg TEQ/g lipid. To increase the sample size, girls of the same age from these cohorts were also included in the dataset. As the direct analysis of PCDD/Fs and dioxin-like PCBs (DL-PCBs) was not possible due to limited serum volume available, TEQ-levels were estimated based on the levels of 9 most prevalent PCB congeners, which could be detected from a much smaller serum volume (200 µl). For this estimation, we created a hierarchical Bayesian regression model that was based on our previous PCDD/F and PCB data from 535 human milk samples collected in 2000, 2005 and 2010 from 3 Finnish cities. For quality control of the selected approach, we measured PCDD/Fs and PCBs from pooled blood samples of young male blood donors and compared measured TEQs with pools' estimated TEQs.

2. Materials and methods

2.1. Serum samples, human milk samples and pooled blood samples

Serum samples (200 µl) of pre-pubertal boys and girls were collected from two cohorts. Details of the samples are given in Table 1. In the MULTIEPIGEN study (https://cordis.europa.eu/project/id/742927), serum samples were collected in April–August 2018, from 12 boys and 24 girls 7–9 years old from comprehensive geographical coverage of Finland. Triglycerides and total cholesterol were also determined from these samples, which enabled the calculation of total serum lipids according to equation of (Phillips et al., 1989).

In the Extended Finnish PASTURE Cohort (LUKAS2) (Karvonen et al., 2009), serum samples were collected in September 2014–November 2015, from 78 boys and 70 girls 10 years of age from the city of Kuopio and surrounding countryside. As serum lipids were not determined in the LUKAS2 samples, the median of MULTIEPIGEN total serum lipids of (0.51%) was assumed for all EFPC samples.

Table 1. Background information for serum samples collected from different cohorts.

Cohort/City		Year of birth	Age at sampling	Nr. of samples
MULTIEPIGEN				
Helsinki				
	Female	2009–2011	7–9	2
Kuopio				
	Male	2011	7	3
	Female	2009–2010	8–9	8
Oulu				
	Male	2009–2010	8–9	2
	Female	2009–2011	7–9	6
Tampere				
	Male	2009–2011	7–9	5
	Female	2009–2011	7–9	7
Turku				
	Male	2009–2011	7–9	2
	Female	2009	9	1
MULTIEPIGEN 7-9 years total				36
LUKAS2 (Kuopio and surrounding countryside)				

Male	2004	10	78
Female	2004	10	70

To create a regression model on the relationship of 9 PCBs to PCDD/F TEQ and total TEQ, we used our previous data on human milk samples collected in 2000 (n=113), 2005 (n=220) and 2010 (n=202) from southern (Helsinki), central (Kuopio) and northern (Rovaniemi) Finland. Background information and (unpublished) summary of PCDD/F- and PCB-concentrations measured from these samples are given in Supplementary Information (SI) Table S1.

For quality control of the Bayesian estimation approach, blood samples of volunteer male donors aged 18–20 years from the cities of Helsinki (n=22), Tampere (n=20) and Turku (n=18) were collected by the Finnish Red Cross in February–March 2019. The pooled sample for each city was created by mixing 10 ml of blood from each donor and analysed for PCBs and PCDD/Fs from 100 ml aliquot. We assumed congener profiles of PCDD/Fs and PCBs in these youngest possible volunteer male donors (18–20 years) to be the most representative available to those of young boys under scrutiny.

2.2. Chemical analysis of serum, milk and whole blood samples

From the 200 µl serum samples 9 PCB congeners were measured (PCB 74, 99, 118, 138, 153, 156, 170, 180 and 187). PCBs 52, 101 and 183 were also measured but excluded from further analyses, because of high number of non-detects. Method consisted of liquid-liquid extraction, silica column clean-up and analysis by Agilent 7010 gas chromatograph triple quadrupole mass spectrometer (GC-MS/MS) (Koponen et al., 2013).

Standard extraction and clean up procedures used for PCDD/Fs and PCBs have been described earlier for mothers' milk (Kiviranta et al., 2004; Main et al., 2007) and pooled blood (Kiviranta et al., 2002) samples. Human milk samples were analysed with Agilent 6890 gas chromatograph

connected to Waters Autospec Ultima high resolution mass spectrometer (GC-HRMS) and pooled blood samples (100 ml) with Agilent 7010 GC-MS/MS. Analysis of both mothers' milk and pooled blood samples were conducted according to requirements laid down in the Commission Regulation (EU) 2017/644 (EU, 2017). All methods used have been described in more detail in Supplementary Information.

2.3 Statistical testing of PCBs analysed from children's serum samples

Basic statistical tests to compare measured concentrations 9 PCBs within and between MULTIEPIGEN and LUKAS2 (mean, median, percentiles, t-test) were performed with IBM SPSS Statistics 25. In the calculation of means, medians and percentiles of measured PCB concentrations from MULTIEPIGEN and LUKAS2 cohorts, results below level of detection (LOD) were replaced with LOD/2.

2.4 Estimation of PCDD/F TEQ and total TEQ in serum samples using hierarchical Bayesian regression model

PCDD/F and PCB congener data from all human milk samples (n=535) and pooled blood donor samples (n=3) were used to estimate the PCB congener coefficient distributions. These coefficient distributions were then used to predict individual posterior distributions of PCDD/F TEQs and total TEQs for each of the 184 children from MULTIEPIGEN and LUKAS2 studies.

To do this, TEQ values (separately for PCDD/F and PCB TEQ concentrations) were predicted using linear regression analysis of log-transformed PCB concentrations. The regression formula was

$$\ln y_i \sim N(\sum \beta_j \ln x_{i,j}, \tau),$$

where y is the TEQ concentration, i is an index for individuals, j is an index for PCB congeners, N is a normal distribution with parameters mean and precision, β is a congener-specific coefficient, x is a congener concentration, and τ is the precision of the distribution. We used hierarchical Bayesian

regression with Gibbs sampling (Gelman et al., 2004) rather than frequentist linear regression, because we were interested in the posterior TEQ distributions of individual people given their personal PCB profiles.

Uninformative normal priors were used for β_j for each congener and uninformative gamma priors were used for τ for PCDD/F TEQ and PCB TEQ concentrations. The total TEQ was calculated as the sum of PCDD/F TEQ and PCB TEQ. The parameters β and τ were assumed to apply to all study groups: children, blood donors, and mothers.

Blood donors and mothers were added to the modelled data set twice: first with the measured TEQ value to estimate the parameter distributions, and then without the measured TEQ value to predict individual posterior distributions about what the TEQ estimates would likely be if they were not known.

Other independent variables than PCB concentrations were not used, because the explanatory power of the model was already very good (R^2 ca. 0.9 for total TEQ, see supplementary information Figure S1).

Regression analyses were performed using R statistical software (version 3.6.2, cran.r-project.org) and JAGS Gibbs sampler (version 4.3.0).

The model code and synthetic data for testing is available at Github (https://github.com/jtuomist/dioxdisthuman).

3. Results

3.1. Concentrations of PCBs measured in the serum of MULTIEPIGEN and LUKAS2 children

Overall, the concentrations of PCBs in the serum samples from MULTIEPIGEN and LUKAS2 cohorts were very low (Table 2). For 9 PCB congeners (74, 99, 118, 138, 153, 156, 170, 180 and 187) mean and median concentrations were >LOD. These 9 congeners were included in the further

analysis. However, even of these 9 congeners, mean concentrations of PCBs 74, 99, 156, 118 and 187 were below or around the LOQ of 5 pg/ml (Table 2).

Table 2. Concentrations of PCBs (pg/ml) measured in MULTIEPIGEN and LUKAS2 serum samples (n=184).*

Congener	% > LOD	Mean	Median	10th perc.	90th perc.
PCB52	1.8	<LOD	<LOD	<LOD	<LOD
PCB74	67	3.2	2.4	<LOD	5.3
PCB99	73	3.3	2.9	<LOD	5.6
PCB101	1.8	<LOD	<LOD	<LOD	<LOD
PCB118	95	5.3	4.5	2.7	8.8
PCB138	99	21	18	7.6	41
PCB153	100	38	31	12	72
PCB156	60	3.3	2.7	<LOD	7.1
PCB-170	96	10	8.4	2.7	21
PCB180	100	23	19	5.9	48
PCB183	34	<LOD	<LOD	<LOD	3.3
PCB187	85	5.6	4.5	<LOD	11

*LOD = 2 pg/ml and LOQ = 5 pg/ml for all congeners. In the calculation of means, medians and percentiles results <LOD were replaced with LOD/2.

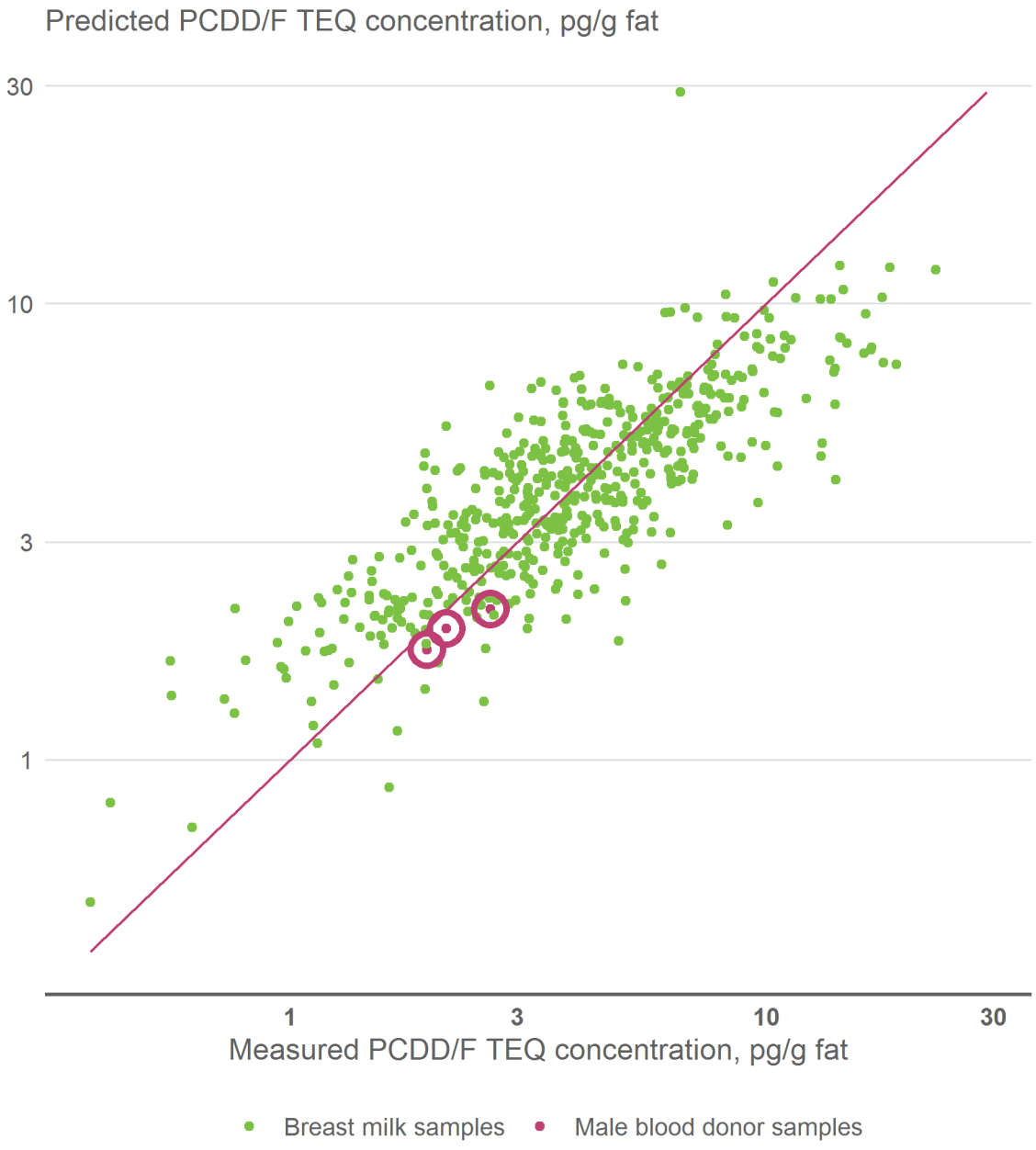
Mean and median concentrations of ∑PCB-9 in MULTIEPIGEN and LUKAS2 cohorts by sex are given in SI Table S2. Due to 3 extreme samples, mean of ∑PCB-9 in MULTIEPIGEN boys (40 ng/g lw) was 44% larger than in MULTIEPIGEN girls (28 ng/g lw), but difference in the median of ∑PCB-9 was only 18%. Overall, as no statistically significant within cohort difference in serum ∑PCB9 levels between boys and girls were found in 2-sided t-test in either MULTIEPIGEN or

LUKAS2, we considered it appropriate to include also girls in the Bayesian analysis. However, differences between cohorts were borderline or significant (SI Table S3).

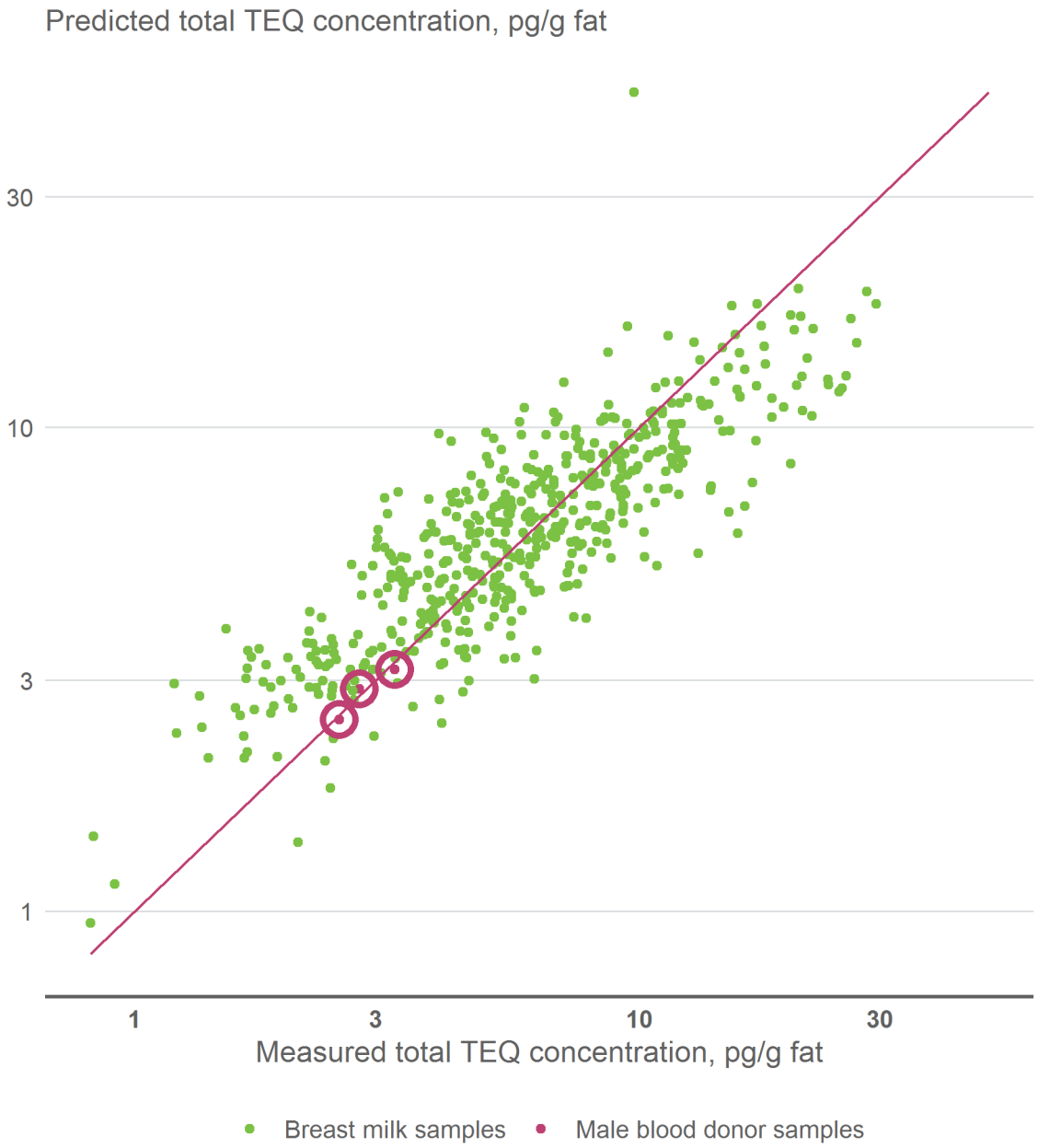
3.2. TEQ-prediction power of PCBs for human milk and pooled blood samples

The power of 9 PCBs to predict TEQs was tested in 3 different ways using human milk samples. Results are shown in SI Figure S1. For PCDD/F TEQ, PCB-TEQ and total TEQ, the best correlation is obtained when congener-specific concentration data of all 9 PCBs contribute to the model. Obviously the fit for PCB-TEQ was better than for PCDD/F TEQ, but slightly surprisingly the fit for total TEQ was similar to or even better than for PCB TEQ. Overall, information rich models (congener-specific data of all 9 PCBs as predictors) are superior for all estimated TEQs compared to single congener or sum of congeners.

Figure 1 shows measured versus predicted PCDD/F TEQ and total TEQ using 9 PCBs as predictors for human milk and pooled blood samples. For human milk samples, models appear to slightly underestimate both TEQs at low concentrations and overestimate at high concentrations. However, between 3 and 10 pg/g that encloses the NOAEL of 7 pg total TEQ/g lipid, the fit is satisfactory. Pooled blood samples used for quality control are relatively close to one-to-one line in Figure 1. Measured and predicted TEQ-concentrations are shown numerically in SI Table S4. Compared to measured lower bound concentrations, predicted concentrations of PCDD/F TEQs range from 84% to 94% and those of total TEQs from 99% to 106%, respectively.


Predicted PCDD/F TEQ concentration, pg/g fat
30
10
3
1
1
3
10
30
Measured PCDD/F TEQ concentration, pg/g fat
Breast milk samples
Male blood donor samples

237 A)



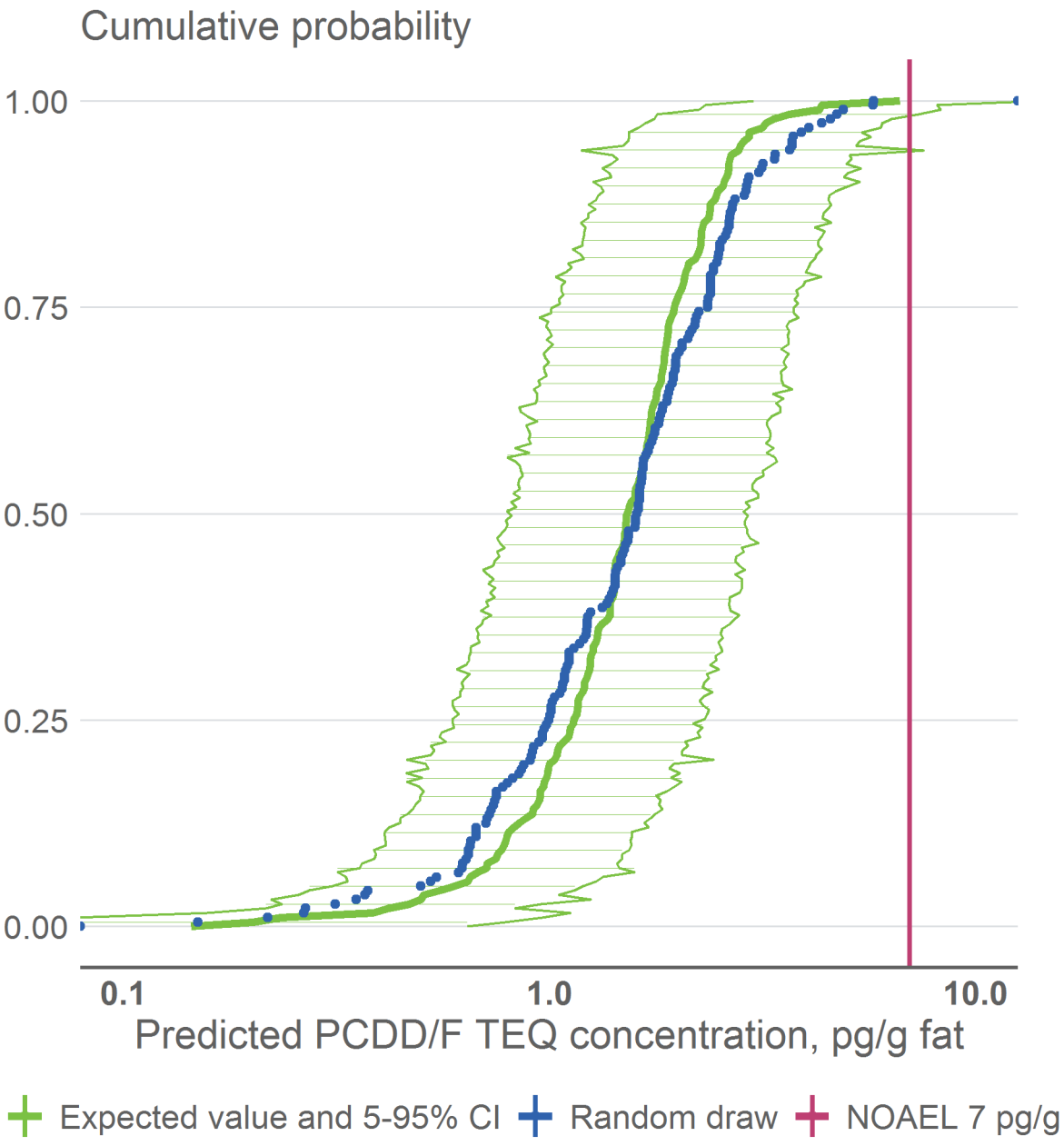
238 B)

239 Figure 1. Prediction accuracy of 9 PCBs for A) PCDD/F TEQ and B) total TEQs with Bayesian

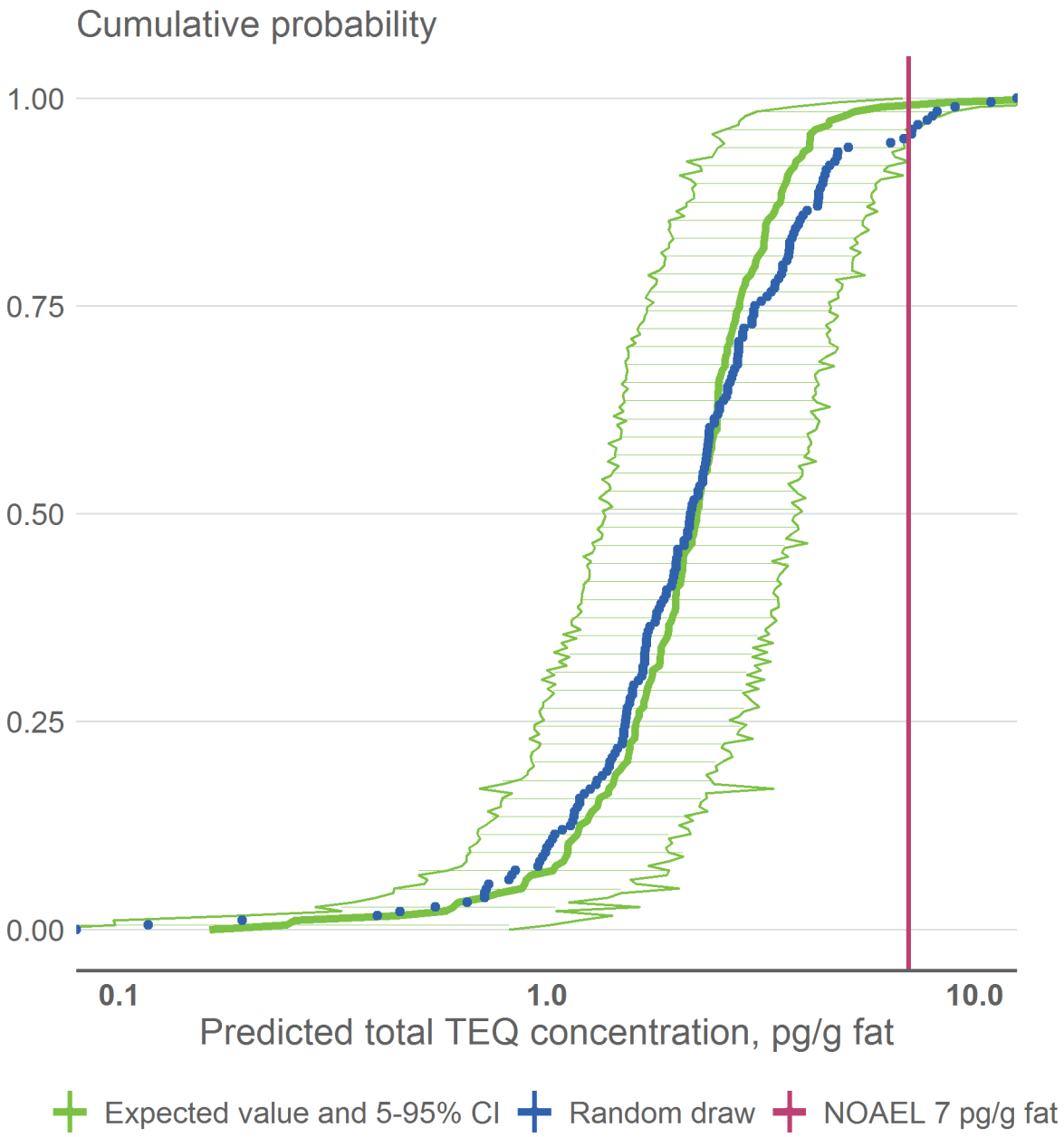
240 hierarchical regression model for human milk (green dots) and pooled blood (red circles) samples.

3.3 PCDD/F TEQ and total TEQ concentrations in the serum of MULTIEPIGEN and LUKAS2 children, estimated by Bayesian hierarchical regression model

Cumulative probability distribution of predicted PCDD/F TEQs and total TEQs in children's serum from MULTIEPIGEN and LUKAS2 combined compared to NOAEL of 7.0 pg TEQ/g lipid are shown in Figure 2. All expected values for PCDD/F TEQ and 98,9% of expected total TEQ values were below NOAEL. However, random draws from each child's probability distribution is a more realistic approach to evaluate NOAEL exceedance. For 0.5% and 2.7 % of the children PCDD/F TEQ and total TEQ was exceeded, respectively.


Cumulative probability
1.00
0.75
0.50
0.25
0.00
0.1
1.0
10.0
Predicted PCDD/F TEQ concentration, pg/g fat
Expected value and 5-95% CI
Random draw
NOAEL 7 pg/g

A)



B)

Figure 2. Cumulative probability distribution of predicted A) PCDD/F TEQs and B) total TEQs in children's serum from MULTIEPIGEN and LUKAS2 combined. Green line = Expected value for each child; Green "saw-edged" line =90% CI (5-95%) individual

distributions of expected value; Blue line = Random draw from the probability distributions of each child. Random draws points are independently arranged in increasing order, and they do not refer to the same individual as expected value and its CI on the same row.

4. Discussion

The aim of this study was to estimate whether the NOAEL of 7.0 pg/g lipid identified from the Russian study is exceeded for PCDD/F or total TEQ among 7–10 year old Finnish children. When the estimated TEQ-concentration for each child was randomly drawn from individual probability distributions, PCDD/F TEQ exceeded NOAEL in 0.5% and total TEQ in 2.7% of subjects. These results and the overall decrease of human exposure imply that risk management actions following the drastically decreased TWI proposed by the CONTAM Panel should be carefully considered. If relatively remote risks define the dietary recommendations, indirect consequences on total dietary risks may be great. For example, exclusion of fish from the market in the situation where PCDD/F levels in the serum of boys potentially affected are already largely below the NOAEL would only lead to losses of fish related health benefits for consumers.

The approach selected to estimate the levels of PCDD/F TEQ and total TEQ in the blood of boys around 9 years of age has to be seen in the context where serum available per individual is barely enough for the measurement of major PCBs with a highly sensitive analytical method. Total volume of serum available from all 184 samples received for this study could have enabled congener specific analysis of PCDD/Fs and mono-ortho-PCBs from a single pooled sample, but individual variation in concentrations would have been lost. Thus, we

utilized our extensive dataset from mothers' milk to model the relationship between 9 PCBs measurable from small volume of serum and TEQ concentrations.

In the construction of hierarchical Bayesian regression model we used mothers' milk results from years 2000, 2005 and 2010. These birth years match closely the birth years of the blood donors (1999-2001), and children from LUKAS2 (2004) and MULTIEPIGEN (2009-2011). There is some variation in the PCDD/F- and PCB-congener profiles between serum/blood and breast milk. For example, in our milk samples median contribution of PCB-126 to total TEQ was 22–25% (10^{th}–90^{th} percentiles 16–33%) and median contribution of PCB-TEQ to total TEQ was 30–34% (10^{th}–90^{th} percentiles 24–43%) depending on the year. In pooled blood samples PCB-126 contributed only 12–16% to the lower bound of total TEQ, and PCB-TEQ contributed 20–24% to total TEQ. Lower contribution of PCB 126 to total TEQ in blood compared to breast milk is in agreement with results from Japanese paired samples (Todaka et al., 2010).

These differences in congener profiles are possibly reflected in the slight underestimation of hierarchical Bayesian regression model predicted PCDD/F TEQs (84–99%) from pooled blood samples. However, the prediction accuracy was considered satisfactory and proved the ability of hierarchical Bayesian regression model to predict PCDD/F TEQ also from MULTIEPIGEN and LUKAS2. As Red Cross donors were 10 years older than the boys of critical age, our underlying assumption is that the half-life of 9 PCB congeners are close to those PCDD/F congeners that make up most of the PCDD/F TEQ. Congeners that contributed 80% to PCDD/F TEQ were 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD and 2,3,4,7,8-PeCDF. The elimination half-life of PCDD TEQ has been estimated at 8.7 years (EFSA 2018) and that of

2,3,4,7,8-PeCDF 7–20 years depending on the study (Flesch-Janys et al., 1996; Rohde et al., 1999; Ogura, 2004; Milbrath et al., 2009). The estimates of intrinsic adult elimination half-lives at background levels for PCB congeners 118, 138, 153, 170, 180, 187 range from 9 to 15 years (Ritter et al., 2009). Furthermore, (Grandjean et al., 2008) found no indication that intrinsic elimination half-lives of PCBs depend on age or are shorter in children than in adults after correcting for the effect of growth. Thus, half-lives of PCDD/F TEQ and 9 PCBs appear reasonably similar to justify our assumption.

For random draw, the proportion of children exceeding the NOAEL was increased from 0.5% for PCDD/F TEQ to 2.7% for total TEQ. Percentages remain small, but relative increase from PCDD/F TEQ to total TEQ was large. However, the interpretation of total TEQ is somewhat complicated. In the EFSA risk assessment there was also a strong recommendation to reevaluate the TEF-value of 0.1 assigned for PCB-126. Observations from *in vitro* studies with human cells show that PCB-126 is much less potent in humans than suggested by the WHO2005-TEF of 0.1.. This was seen by EFSA to be reflected in the critical study on Russian boys, where PCDD/F TEQ ($p=0.04$) but not total TEQ ($p=0.61$) was associated with decreased sperm concentration (EFSA 2018).

Small percentage of children exceeding the NOAEL may on part depend on the age of children in our cohorts. We combined MULTIEPIGEN and LUKAS2 children in the Bayes model due to limited number of samples available from MULTIEPIGEN (n=36) even if mean ΣPCB9 (ng/g lipid) in MULTIEPIGEN children was significantly ($p=0.001$) higher than in LUKAS2. This difference can largely be explained by growth dilution as the median ΣPCB9 concentration in MULTIEPIGEN subjects converges with increasing age from 7 years (40

ng/g lipid, n=7) to 8 years (27 ng/g lipid, n=9) and to 9 years (23 ng/g lipid, n=19) towards to the median ΣPCB9 concentration (17 ng/g lipid, n=148) in LUKAS2 subjects all 10 years of age. However, at the age of 9 years only a slightly larger fraction of LUKAS2 children would have exceeded the NOAEL of 7.0 pg/g lipid based on the shape of PCDD/F and total TEQ distributions (Figure 2A and 2B).

The TWI of 2 pg TEQ/kg bw for the sum PCDD/Fs and PCBs proposed by the CONTAM Panel was based on the accumulation models used (EFSA, 2018). Regarding the model used for boys in the EFSA risk assessment (milk 5.9 pg TEQ/g for 1 year + intake 4 pg TEQ/kg/week for 8 years results in serum level of 7 pg TEQ/g lipid), our data on PCDD/F basis supports it relatively well. Median PCDD/Fs in breast milk around 2005–2010 were 2–4 pg TEQ/g lipid (Table S1). Based on the Finnish intake study (Kiviranta et al., 2001), our fish data (Airaksinen et al., 2018) and recent Swedish intake data (Livsmedelverket, 2017), adult dietary PCDD/F intake around the years 2010–2018 could be estimated at 2–4 pg TEQ/kg bw/week that would imply an intake of 4–8 pg TEQ/kg bw/week for children. However, considering that this intake is likely overestimated due to lower consumption of Baltic Sea fatty fish among children compared to the whole population estimate almost 20 years ago (Kiviranta et al., 2004), our estimated median serum PCDD/F TEQ levels of 2–3 pg/g lipid around 10 years of age is in good agreement with the EFSA model. On the contrary, the long term maternal accumulation model of EFSA (milk 5.9 pg TEQ/g lipid for 1 year + intake 2 pg TEQ/kg/week for 34 years results in milk level of 5.9 pg TEQ/g lipid) seems largely overestimated. Our unpublished median milk PCDD/F concentration in primipara mothers in 1987 was 23 pg TEQ/g lipid, calculated intake around 2000 was 5–6 pg TEQ/ kg bw/week

(Kiviranta et al., 2001; Kiviranta et al., 2004) and an estimate of PCDD/Fs in the milk of a 33 year old primipara mother in year 2020 is ≤2.5 pg TEQ/g lipid extrapolated from 2010 milk data assuming 4–5% annual decrease. Thus, even if our intake estimate from 2000 would be 50% overestimated for women entering the reproductive age, the maternal accumulation model of EFSA would still be clearly overprotective compared to our measured levels in breast milk from 1987 through 2010 and estimated levels in 2020. This also calls for caution in risk management options considering the neurodevelopmental benefits of maternal fish consumption during pregnancy and lactation.

This study has some limitations. Very small amount of serum was available from each child and it was thus not possible to measure PCDD/F TEQ and total TEQ from pooled serum samples of children. It would have been useful to compare the pool concentrations with the mean of hierarchical Bayesian regression estimates. Children in LUKAS2 were 1–2 years older than in the critical Russian study that could have resulted in slight underestimation in the proportion of children exceeding the NOAEL of 7.0 pg/g lipid. The number of boys especially in MULTIEPIGEN was limited and we merged the cohorts as pre-pubertal PCDD/F and PCB levels within cohorts were not significantly different between sexes. Finally, we did not have serum lipids measured from LUKAS2, but used the median of MULTIEPIGEN total lipids for all LUKAS2 subjects. However, this was assumed to have only a minor impact on results as the range of total lipids in MULTIEPIGEN (and supposedly in LUKAS2 also) was narrow (5^{th}–95^{th} percentile 0.43–0.64%) and was expected to be similar also in LUKAS2.

5. Conclusions

We used a hierarchical Bayesian regression model to estimate PCDD/F TEQs and total TEQs in 7–10 year old Finnish children's serum from measured serum levels of major PCBs. More than 99% of children were estimated to have serum PCDD/F TEQ concentration below the NOAEL of 7.0 pg/g lipid identified from the critical Russian study for impaired semen quality later in life. For total TEQ, the respective estimate was more than 97%. Due to cohorts used, the mean age of our children was slightly less than 10 years compared to 8–9 years in the critical Russian study. Our estimate is thus likely a slight underestimate of the true concentrations in 8–9 year old Finnish boys. However, our estimate is accurate enough to conclude that possible risk management actions following the drastically decreased TWI of 2 pg TEQ/kg bw/week established by the CONTAM Panel should be carefully considered before acceptance. There are little if any potential health risks that can be avoided with decreased maximum levels in foods, but a plenty of health benefits to lose if fish consumption is decreased as a result lowered maximum levels. We recommend more biomonitoring studies especially on the levels of PCDD/Fs and PCBs in breast milk as such studies are the easiest to conduct. Also analysis of PCDD/Fs and PCBs in the serum of young boys either from pooled samples or estimated using regression models as presented here is warranted. Risk management actions should also rely on measurements of sensitive target population concentrations, not solely on modelling.

Declaration of interest

None

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References

Airaksinen, R., Jestoi, M., Keinänen, M., Kiviranta, H., Koponen, J., Mannio, J., Myllylä, T., Nieminen, J., Raitaniemi, J., Rantakokko, P., Ruokojärvi, P., Venäläinen, E.-V., P.J., V., 2018. Changes in the levels of enviromental contaminants of Finnish wild caught fish. Prime Minister´s Office, Helsinki, Finland.

EFSA, 2012. Update of the monitoring of levels of dioxins and PCBs in food and feed. EFSA Journal 2012;10(7):2832

EFSA, 2018. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. EFSA Journal 2018;16(11):5333.

European Commission, 2017. COMMISSION REGULATION (EU) 2017/644 of 5 April 2017 laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No 589/2014. Official Journal of the European Union L 92/9-34.

European Commission, 2011. COMMISSION REGULATION (EU) No 1259/2011 of 2 December 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for dioxins, dioxin-like PCBs and non dioxin-like PCBs in foodstuffs. Official Journal of the European Union L 320/18-23.

Flesch-Janys, D., Becher, H., Gurn, P., Jung, D., Konietzko, J., Manz, A., Papke, O., 1996. Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans in occupationally exposed persons. J Toxicol Environ Health. 47, 363-378. doi: 310.1080/009841096161708.

Gelman, A., Carlin, J.B., Stern, H.S., Rubin, D.B. 2004. Bayesian Data Analysis (second ed.). Boca Raton, Florida: CRC Press. ISBN 1-58488-388-X.

Grandjean, P., Budtz-Jorgensen, E., Barr, D.B., Needham, L.L., Weihe, P., Heinzow, B., 2008. Elimination half-lives of polychlorinated biphenyl congeners in children. Environ Sci Technol. 42, 6991-6996. doi: 6910.1021/es800778q.

Karvonen, A.M., Hyvärinen, A., Roponen, M., Hoffmann, M., Korppi, M., Remes, S., von Mutius, E., Nevalainen, A., Pekkanen, J., 2009. Confirmed moisture damage at home, respiratory symptoms and atopy in early life: a birth-cohort study. Pediatrics. 124, e329-338. doi: 310.1542/peds.2008-1590.

Kiviranta, H., Hallikainen, A., Ovaskainen, M.L., Kumpulainen, J., Vartiainen, T., 2001. Dietary intakes of polychlorinated dibenzo-p-dioxins, dibenzofurans and polychlorinated biphenyls in Finland. Food Addit. Contam. 18, 945-953. doi: 10.1080/02652030110057134

Kiviranta, H., Ovaskainen, M.L., Vartiainen, T., 2004. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environment international 30, 923-932. doi: 10.1016/j.envint.2004.03.002

Kiviranta, H., Vartiainen, T., Tuomisto, J., 2002. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 110, 355-361. doi: 310.1289/ehp.02110355.

Koponen, J., Rantakokko, P., Airaksinen, R., Kiviranta, H., 2013. Determination of selected perfluorinated alkyl acids and persistent organic pollutants from a small volume human serum sample relevant for epidemiological studies. Journal of Chromatography A 1309, 48-55. doi: 10.1016/j.chroma.2013.07.064

Leijs, M.M., Koppe, J.G., Olie, K., van Aalderen, W.M., Voogt, P., Vulsma, T., Westra, M., ten Tusscher, G.W., 2008. Delayed initiation of breast development in girls with higher prenatal dioxin exposure; a longitudinal cohort study. Chemosphere. 73, 999-1004. doi: 1010.1016/j.chemosphere.2008.1005.1053.

Link, B., Gabrio, T., Zoellner, I., Piechotowski, I., Paepke, O., Herrmann, T., Felder-Kennel, A., Maisner, V., Schick, K.H., Schrimpf, M., Schwenk, M., Wuthe, J., 2005. Biomonitoring of persistent organochlorine pesticides, PCDD/PCDFs and dioxin-like PCBs in blood of children from South West Germany (Baden-Wuerttemberg) from 1993 to 2003. Chemosphere. 58, 1185-1201. doi: 1110.1016/j.chemosphere.2004.1109.1061.

Livsmedelverket, 2017. Swedish Market Basket Survey 2015 – per capita-based analysis of nutrients and toxic compounds in market baskets and assessment of benefit or risk. Livsmedelsverkets rapportserie nr 26/2017. The National Food Agency of Sweden, Uppsala.

Main, K.M., Kiviranta, H., Virtanen, H.E., Sundqvist, E., Tuomisto, J.T., Tuomisto, J., Vartiainen, T., Skakkebaek, N.E., Toppari, J., 2007. Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. Environmental health perspectives 115, 1519-1526. doi: 10.1289/ehp.9924

Milbrath, M.O., Wenger, Y., Chang, C.W., Emond, C., Garabrant, D., Gillespie, B.W., Jolliet, O., 2009. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ Health Perspect. 117, 417-425. doi: 410.1289/ehp.11781.

Minguez-Alarcon, L., Sergeyev, O., Burns, J.S., Williams, P.L., Lee, M.M., Korrick, S.A., Smigulina, L., Revich, B., Hauser, R., 2017. A Longitudinal Study of Peripubertal Serum Organochlorine Concentrations and Semen Parameters in Young Men: The Russian Children's Study. Environ Health Perspect 125, 460-466. doi: 10.1289/EHP25

Ogura, 2004. Half-life of each dioxin and PCB congener in the human body. Organohalogen Compounds 66, 3329–3337.

Papadopoulou, E., Kogevinas, M., Botsivali, M., Pedersen, M., Besselink, H., Mendez, M.A., Fleming, S., Hardie, L.J., Knudsen, L.E., Wright, J., Agramunt, S., Sunyer, J., Granum, B., Gutzkow, K.B., Brunborg, G., Alexander, J., Meltzer, H.M., Brantsaeter, A.L., Sarri, K., Chatzi, L., Merlo, D.F., Kleinjans, J.C., Haugen, M., 2014. Maternal diet, prenatal exposure to dioxin-like compounds and birth outcomes in a European prospective mother-child study (NewGeneris). Sci. Total Environ. 484, 121-128. doi: 10.1016/j.scitotenv.2014.03.047

Phillips, D.L., Pirkle, J.L., Burse, V.W., Bernert, J.T., Jr., Henderson, L.O., Needham, L.L., 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol. 18, 495-500. doi: 410.1007/bf01055015.

Ritter, R., Scheringer, M., MacLeod, M., Moeckel, C., Jones, K.C., Hungerbuhler, K., 2009. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. Environ Health Perspect 119, 225-231. doi: 10.1289/ehp.1002211

Rohde, S., Moser, G.A., Papke, O., McLachlan, M.S., 1999. Clearance of PCDD/Fs via the gastrointestinal tract in occupationally exposed persons. Chemosphere. 38, 3397-3410. doi: 10.1016/s0045-6535(98)00551-7

SCF, 2001. Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCB in food (update based on the new scientific information available since the adoption of the SCF opinion of 22 November 2000) (adopted on 30 May 2001). European Commission, Scientific Committee on Food.

Starling, P., Charlton, K., McMahon, A.T., Lucas, C., 2015. Fish Intake during Pregnancy and Foetal Neurodevelopment-A Systematic Review of the Evidence. Nutrients 7, 2001-2014. doi: 10.3390/nu7032001

Todaka, T., Hirakawa, H., Kajiwara, J., Hori, T., Tobiishi, K., Yasutake, D., Onozuka, D., Sasaki, S., Miyashita, C., Yoshioka, E., Yuasa, M., Kishi, R., Iida, T., Furue, M., 2010. Relationship between the concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls in maternal blood and those in breast milk. Chemosphere 78, 185-192. doi: 10.1016/j.chemosphere.2009.09.047

Turunen, A.W., Jula, A., Suominen, A.L., Männisto, S., Marniemi, J., Kiviranta, H., Tiittanen, P., Karanko, H., Moilanen, L., Nieminen, M.S., Kesäniemi, Y.A., Kähönen, M., Verkasalo, P.K., 2013. Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis. Environ Res 120, 43-54. doi: 10.1016/j.envres.2012.09.007

Turunen, A.W., Verkasalo, P.K., Kiviranta, H., Pukkala, E., Jula, A., Mannisto, S., Rasanen, R., Marniemi, J., Vartiainen, T., 2008. Mortality in a cohort with high fish consumption. Int. J. Epidemiol. 37, 1008-1017. doi: 10.1093/ije/dyn117

Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A., Haws, L., Rose, M., Safe, S., Schrenk, D., Tohyama, C., Tritscher, A., Tuomisto, J., Tysklind, M., Walker, N., Peterson, R.E., 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci. 93, 223-241. doi: 210.1093/toxsci/kfl1055.

Supplementary information

Estimated PCDD/F TEQ and total TEQ concentrations in the serum of 7–10 year old Finnish children

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Analysis of PCBs from serum

From the 200 µl serum samples (Young Finns Study and Extended Finnish Pasture Cohort) 9 PCB congeners (74, 99, 118, 138, 153, 156, 170, 180 and 187) were measured. Sum of these PCBs is denoted as ∑PCB-9 in tables below. The method has been described earlier in detail (Koponen et al. 2013). In brief, ethanol and 13C-labelled internal standards of each compound in toluene were added to samples (200 µl) in test tubes and mixed to precipitate the proteins and equilibrate internal standards. Dichloromethane-hexane (1:4) was added for extraction followed by activated silica to bind the sample water, ethanol and precipitate. Samples were mixed, and layers were allowed to separate. The upper dichloromethane-hexane layer was poured to a solid phase extraction cartridge (SPE cartridge) containing from bottom to top 10% AgNO3 impregmented silica and a mixture of Na2SO4 and silica. The lower layer in the test tube was extracted again with dichloromethane-hexane that was also poured to SPE-cartridge. Elution of SPE-cartridges was continued with dichloromethane-hexane and the eluate was concentrated to 15-20 µl for gas chromatography - high triple quadrupole mass spectrometry (GC-MS/MS) analysis. The instrument used was Agilent 7010 GC-MS/MS system (Wilmington, DE, USA) GC column was DB-5MS UI (J&W Scientific, 20m, ID 0.18 mm, 0.18 µm film).

As control serum sample NIST SRM 1958 with known concentrations of PCBs was analysed in each batch (n=8) of samples. In addition, due to generally low levels of POPs in YFS and EFPC samples, also SRM 1958 diluted 1/10 with New Born Calf Serum (Dil-SRM 1958) was analysed in each sample batch. Mean accuracy (91-110% of SRM 1958 certified/reference concentrations and 85-102% of calculated concentrations in diluted SRM 1958) and precision (co-efficient of variation (CV) ≤ 4.1% for SRM 1958 and ≤ 5.4% for Dil-SRM 1958) were acceptable for measured PCBs in control samples. Limit of quantitation (LOQ) was 5 pg/ml and limit of detection (LODs) 2 pg/ml for 9 PCBs.

Analysis of PCDD/Fs and PCBs mothers' milk and pooled blood samples

From the mothers' milk and pooled blood samples (100 ml), 17 dioxin congeners and 23 PCBs (including 12 dioxin like PCBs and 11 other PCBs including the above 9 PCBs) were analysed. Sample pre-treatment included liquid-liquid extraction, gravimetric determination of lipid content, multilayer silica column cleanup and fractionation by activated carbon column as previously described for milk (Kiviranta et al., 2004; Main et al., 2007) and blood (Kiviranta et al. 2002). Cleaned milk samples were analysed with Waters Autospec Ultima high resolution mass spectrometer (GC-HRMS) and pooled blood samples with Agilent 7010 GC-MS/MS. GC column

was DB-5MS UI (J&W Scientific, 60m, ID 0.25 mm, 0.25 μm film) in both cases. 13C-labelled internals standards of each congener were used for quantification. LOQs of each congener were calculated using the "signal/noise ratio of 3:1" –approach for mothers' milk samples and using the "lowest concentration point on a calibration curve" –approach for pooled blood samples as laid down in the Commission Regulation (EU) 2017/644 (EU 2017) due to instrumental techniques used in each matrix, respectively.

Regarding the quality control, during the years of milk sample analysis (2001-2011), laboratory participated every year successfully to Interlaboratory Comparison of Persistent Organic Pollutants in food (ILC POPs) since the first round in 2000 (https://www.fhi.no/en/studies/ilc-pop/). For the recent analysis of pooled blood samples, an in-house spiked quality control sample was extracted and analysed with GC-MS/MS that had a recovery of 89% for PCDD/F TEQ, 111% for PCB-TEQ and 88% for the sum of 23 PCBs as compared to long term in-house average, respectively.

Laboratory of chemistry at the Finnish Institute for Health and Welfare is an accredited testing laboratory T077 by Finnish Accreditation Services (FINAS) since 1996. Scope of accreditation includes all of the methods used within this study.

Table S1. Median (10th - 90th percentiles) concentrations of ∑PCB-9 (ng/g lipid), PCDD/F-TEQ and Total-TEQ (pg/g lipid) in mothers' milk samples collected from the cities of Helsinki, Kuopio and Rovaniemi in 2000, 2005 and 2010.

Collection year	City	n	% of 1st-2nd-3rd birth**	Age (range)	∑PCB-9 (ng/g lipid)	PCDD/F-TEQ (pg/g lipid)	Total TEQ (pg/g lipid)
2000							
	Helsinki	56	52 - 34 - 11	31 (26 - 37)	131 (60 - 245)	8.8 (4.2 - 16)	12 (6.1 - 24)
	Kuopio	57	39 - 32 - 25	31 (24 - 36)	93 (47 - 164)	6.3 (3.1 - 13)	9.2 (4.6 - 17)
2005							
	Helsinki	94	41 - 47 - 9	30 (25 - 37)	73 (40 - 140)	4.1 (2.1 - 8.2)	6.8 (3.3 - 14)
	Kuopio	83	48 - 28 - 16	29 (22 - 36)	53 (29 - 101)	3.9 (2.1 - 6.6)	5.5 (3.0 - 9.7)
	Rovaniemi	43	23 - 47 - 14	30 (24 - 39)	61 (33 - 113)	3.4 (2.1 - 6.9)	5.4 (3.4 - 10.4)
2010							
	Helsinki	77	53 - 36 - 8	31 (27 - 37)	57 (28 - 122)	3.3 (1.4 - 5.9)	5.1 (2.3 - 9.1)
	Kuopio	71	32 - 31 - 20	30 (24 - 36)	39 (16 - 76)	2.1 (1.1 - 4.4)	3.1 (1.6 - 6.2)
	Rovaniemi	54	39 - 35 - 17	30 (25 - 37)	48 (23 - 107)	2.6 (1.2 - 5.7)	4.0 (1.9 - 8.1)

* Parity above 3 is what is missing from 100 %

Table S2. Mean and median (10^{th} and 90^{th} percentiles) concentrations of measured ∑PCB-9 (ng/g lipid) by cohort and sex.

Cohort	Year of birth	Age	n	Mean	Median (10^{th} - 90^{th} perc.)
YFS					
Boy	2009-2011	7-9	12	40.3	30.9 (16.7 - 90.5)
Girl	2009-2011	7-9	24	27.9	26.1 (3.61 - 53.1)
EPFC					
Boy	2004	10	78	20.3	16.1 (7.00 - 41.1)
Girl	2004	10	70	17.9	17.2 (8.2 - 30.4)

Table S3. Difference in the ∑PCB9 (ng/g lipid) in boys and girls within and between cohort groups by t-test (p-values).

Cohort		YFS		EFPC*	
	Group	B 7-9 y	G 7-9 y	B 10 y	G 10 y
YFS	B 7-9 y		0.152	0.023	0.012
	G 7-9 y	0.152		0.053	0.011

*No statistically significant difference in ∑PCB9 between boys and girls within EFPC cohort by t-test (p=0.267).

Table S4. Measured concentrations of PCDD/F and PCBs congeners, PCDD/F-TEQs and Total-TEQs in pooled blood samples[#], and estimated PCDD/F-TEQ and Total-TEQ using measured concentrations of 9 PCBs with Bayesian hierarchical regression model.

City	Helsinki	Tampere	Turku
PCDD/Fs (pg/g lipid)			
2,3,7,8-TCDD	<0.56	<0.53	<0.49
1,2,3,7,8-PeCDD	0.82	0.60	0.62
1,2,3,4,7,8-HxCDD	<0.57	<0.50	<0.47
1,2,3,6,7,8-HxCDD	3.79	3.81	3.73
1,2,3,7,8,9-HxCDD	<0.55	<0.49	<0.46
1,2,3,4,6,7,8-HpCDD	8.74	6.20	7.36
OCDD	110	77.9	88.2
2,3,7,8-TCDF	<1.6	<1.5	<1.4
1,2,3,7,8-PeCDF	<1.0	<0.99	<0.91
2,3,4,7,8-PeCDF	2.76	1.76	2.14
1,2,3,4,7,8-HxCDF	1.70	1.23	1.20
1,2,3,6,7,8-HxCDF	1.59	0.88	1.32
1,2,3,7,8,9-HxCDF	<0.34	<0.32	<0.30
2,3,4,6,7,8-HxCDF	<0.48	<0.44	<0.41
1,2,3,4,6,7,8-HpCDF	6.13	4.15	5.30
1,2,3,4,7,8,9-HpCDF	<0.38	<0.34	<0.32
OCDF	<1.4	<1.3	<1.2
non-ortho-PCB (pg/g lipid)			
PCB-77	32.6	29.2	23.5
PCB-81	<1.3	<1.4	<1.1
PCB-126	3.87	3.57	4.42
PCB-169	6.05	6.15	5.33
mono-ortho-PCB (ng/g lipid)			
PCB-105	0.27	0.22	0.22
PCB-114	<0.15	<0.14	<0.13
PCB-118*	1.30	1.07	1.07
PCB-123	<0.18	<0.17	<0.16
PCB-156*	0.67	0.70	0.51
PCB-157	<0.22	<0.21	<0.19
PCB-167	<0.29	<0.27	<0.26
PCB-189	<0.15	<0.13	<0.12
di-ortho-PCB (ng/g lipid)			
PCB-28	0.72	0.73	0.83
PCB-52	0.25	0.26	0.23
PCB-74*	0.54	0.47	0.48

PCB-99*	0.81	0.63	0.70
PCB-101	0.40	0.37	0.32
PCB-138*	5.27	4.41	3.98
PCB-153*	8.41	7.91	6.52
PCB-170*	2.29	2.38	1.73
PCB-180*	4.87	5.24	3.62
PCB-183	0.55	0.48	0.42
PCB-187*	1.54	1.42	1.11
Congener based PCDD/F-TEQ (pg/g lipid)			
lower bound	2.54	1.85	2.04
medium bound	3.01	2.29	2.45
upper bound	3.49	2.74	2.86
Congener based Total-TEQ (pg/g lipid)			
lower bound	3.18	2.45	2.70
medium bound	3.67	2.91	3.12
upper bound	4.15	3.37	3.55
Bayes estimated PCDD/F-TEQ (pg/g lipid)			
	2.14	1.73	1.91
Bayes estimated Total-TEQ (pg/g lipid)			
	3.15	2.52	2.86

Samples from 18-20 year old males from Helsinki (22 donors), Tampere (20 donors) and Turku (18 donors).

*Congener included to 9 PCBs used in modelling.

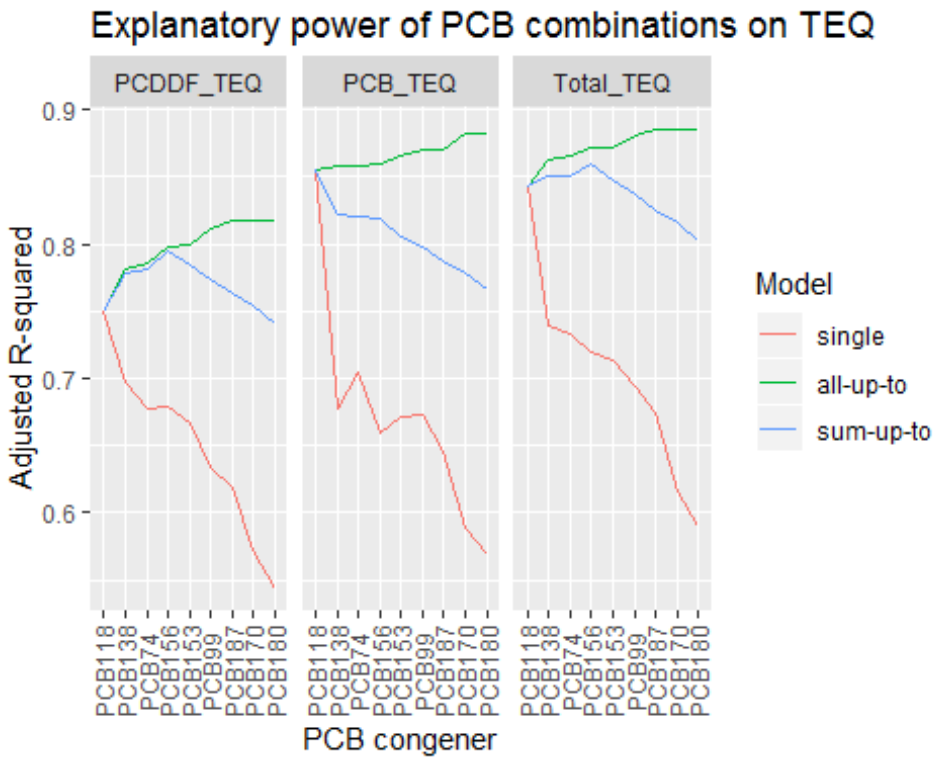

Figure S1. Explanatory power of different combinations of PCBs for TEQ-prediction. Measured PCDD/F and PCB concentrations from human milk (n=535) and pooled blood donor samples (n=3) were used to construct the hierarchical Bayesian regression model that predicted TEQ concentrations using measured PCBs. The congeners on x axis are ordered according to decreasing R^2-value for Total-TEQ prediction by single PCB congener. Single = only one PCB congener concentration as predictor (1 predictor value); all-up-to: congeners added one-by-one to model, but congener-specific concentration data of all added congeners remain in the model (1-9 predictor values); sum-up-to: congener concentrations summed one-by-one on the top of previous congeners in the model (1 predictor value).

References

Kiviranta, H., Vartiainen, T., Tuomisto, J., 2002. Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in fishermen in Finland. Environ Health Perspect. 110, 355-361.

Kiviranta, H., Ovaskainen, M.L., Vartiainen, T., 2004. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environment international 30, 923-932.

Main, K.M., Kiviranta, H., Virtanen, H.E., Sundqvist, E., Tuomisto, J.T., Tuomisto, J., Vartiainen, T., Skakkebaek, N.E., Toppari, J., 2007. Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. Environmental health perspectives 115, 1519-1526.