PAPER III

Person-specific predictions of PCBs in Norwegian Women: Valuable supplements to measurements for understanding of time-variant exposures

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Abstract

Background

Studies on the health effects of polychlorinated biphenyls (PCBs) call for an understanding of past and present human exposure. Time-resolved mechanistic models may supplement information on concentrations in individuals obtained from measurements and/or statistical approaches, if they can be shown to reproduce empirical data.

Objectives

Here we evaluate the capability of one such mechanistic model to reproduce measured of PCB concentrations in individual Norwegian women. We also assess individual life course concentrations.

Methods

Concentrations of four PCB congeners in pregnant women (*n*= 310, sampled in 2007-2009) and postmenopausal women (*n*= 244, sampled in 2004) were compared to person-specific predictions obtained with CoZMoMAN, an emission-based environmental fate and human food-chain bioaccumulation model. Person-specific predictions were also made with statistical models linearly regressing concentrations against dietary and lifestyle variables.

Results

CoZMoMAN accurately reproduced medians and ranges of measured concentrations in the two study groups. Further, the rank correlation between measurements and predictions from both CoZMoMAN and regression analyses was strong (Spearman`s r >0.67). Precision in quartile assignments from predictions was strong overall as evaluated by Weighted Cohen`s Kappa> 0.6. Simulations indicated large inter-individual differences in concentrations experienced in the past.

Conclusions

Agreement between measurements and predictions of concentrations, subject ranking and quartile assignment was good. Contamination histories for individuals predicted by CoZMoMAN revealed variation between study subjects, particularly in the timing of peak concentrations. Realistic a priori assessments of PCB exposures by mechanistic models provide individual PCB exposure metrics that could serve as valuable supplements to measurements.

1. Introduction

Polychlorinated biphenyls (PCBs) have been detected globally and could potentially be harmful to humans and the environment. Emission of PCBs increased from the 1930s and decreased from the 1980s following restrictions or bans on production and use in many countries (Breivik et al., 2010). The exposure of the general population to PCBs has been linked to dietary intakes (Caspersen et al., 2013; Darnerud et al., 2006; Rylander et al., 2012) and time trends in human blood have been shown to reflect those of the emissions (Nøst et al., 2013; Quinn and Wania, 2012). Whereas temporal changes in the human body burden of PCBs have been investigated in general terms (e.g. Quinn and Wania, 2012), knowledge of such longitudinal body burden age-trends (LBATs) within individuals is still limited. Of particular interest are historical exposures in individuals during sensitive life stages (Verner et al., 2008; 2011).

Human bioaccumulation and PCB body burdens as functions of time have been estimated in several pharmacokinetic model approaches of varying design and complexity (Alcock et al. 2000; Moser and McLachlan 2002; Ritter et al. 2009; Verner et al. 2013; 2008). In these studies, time-variant human PCB intake is often obtained by extrapolating point estimates of dietary intake back in time based on historical changes in emissions. The CoZMoMAN model (Breivik et al., 2010) also predicts time-variant human concentrations, but relies on time-variant human dietary intake rates that are linked to the historic emission not by mere scaling but by a mechanistic simulation of environmental fate and human food chain bioaccumulation. These calculations describe how emissions of contaminants are transported and distributed in the environment and predict concentrations in environmental compartments (air, water, soil, sediment) and in the organisms in an aquatic and an agricultural food chain (e.g. grass, cows, fish). Human dietary intake rates are subsequently determined from the time-variant concentrations in air, water and the tissues of food organisms. Using PCB-153 as an example, CoZMoMAN has previously been used to evaluate: i) generational differences in prenatal, postnatal and lifetime exposures (Quinn et al., 2011); ii) associations with age in different sampling years and study designs (Quinn and Wania, 2012); and iii), the impact of transient dietary changes by pregnant women on the pre- and postnatal exposure in their children (Binnington et al., 2014). A similar modelling strategy has also been explored to evaluate PCB exposure time trends in Arctic populations with concurrent transitions in dietary habits (Quinn et al., 2012). These studies can serve to formulate

and test hypotheses concerning the impact of regulatory measures and of behavioural changes on human PCB exposure.

PCB concentrations predicted by CoZMoMAN were within the range of those measured in environmental compartments, organisms and humans in Scandinavia (Breivik et al., 2010; Nøst et al., 2013). Furthermore, CoZMoMAN has reproduced PCB contamination time trends from 1979 to 2007 in Norwegian men (Nøst et al., 2013). Past studies evaluating CoZMoMAN have compared concentrations predicted for a hypothetical "average" person with the observed population means. Individual predictions of PCB concentrations in infants by a different toxicokinetic model strongly correlated with measurements and indicate that reliable person-specific predictions are attainable from such models (Verner et al. 2013). Still, such an evaluation has not been performed for adults. Here we used PCB concentrations measured in pregnant and postmenopausal Norwegian women to evaluate the person-specific predictions in adults from mechanistically derived intake rates. Further, individual LBATs were derived to reconstruct their past exposures. Accompanying predictions from linear regression models aimed to identify potential influential predictors not considered within CoZMoMAN.

2. Material and methods

2.1. Study population

The subjects included in the present study were; i) pregnant women (n= 515) in the Northern Norway mother-and-child contaminant cohort study (MISA), who were enrolled during the second trimester of the pregnancy and donated a blood sample during 2007-2009; ii) postmenopausal women (n= 311) from the general Norwegian population who are participants in the Norwegian women and cancer study (NOWAC) and donated blood samples in 2004. The mean (range) age of the MISA and the NOWAC women was 31 (18-43) and 56 (48-62), respectively. Details and population characteristics for the MISA and NOWAC studies are described by Veyhe et al. (2012) and Waaseth et al. (2008), respectively. The studies were approved by the Regional Committees for Medical Research Ethics.

Demographic, dietary and lifestyle variables were extracted from questionnaires and information on child births for MISA women was extracted from the Norwegian Birth Registry. Daily intakes of a range of food items in grams per day had been calculated from food frequency questionnaires for MISA (Veyhe et al., 2012) and NOWAC women (Skeie et al., 2006).

2.2. Chemical analyses

Concentrations of PCBs in MISA women are reported here for the first time, whereas those in NOWAC women have been published previously by Rylander et al. (2012). The methods employed for the PCB analyses in the MISA and NOWAC studies were similar and have been described in detail in Hansen et al. (2010) and Rylander et al. (2012), respectively. Briefly, internal standards, formic acid and deionised water were added to samples (2 ml serum and 0.75 g plasma for the MISA and NOWAC samples, respectively), who were left in the fridge overnight before being extracted through an HLB solid phase extraction (SPE) column using dichloromethane. Further clean-up involved elution of compounds from Florisil columns with *n*-hexane/dichloromethane. PCBs were identified and quantified in the extracts with a gas chromatograph/mass spectrometer operated in electron impact mode. Assessment of isotopic mass ratios, blank samples and standard reference materials ensured the quality of PCB results.

Lipids were determined enzymatically and the summed amount of lipids was calculated from: Total lipids = 1.677(total – free cholesterol) + free cholesterol + triglycerides + phospholipids (Akins et al., 1989).

2.3. Time-variant model simulations of PCB concentrations

2.3.1. Model input and parameterization

The CoZMoMAN parameterization of the calculation of the time-variant PCB contamination of air, water, soil and sediments and of the organisms making up the agricultural and aquatic food chains for the time period from 1930 to 2010 from historical emissions was identical to that described in Breivik et al. (2010). Time-variant person-specific PCB concentrations were predicted with CoZMoMAN for each woman from birth until sampled by running the model one

time for each person. The model was supplied with person-specific parameters for date of birth of the woman, date of birth and breastfeeding duration for each of her children (maximum four), and daily intake of meat (grams lipid basis), dairy products (grams lipid weight) and fish (grams fresh weight), whereby the latter was assumed to be 35 % piscivorous fish ("cod") and 65 % planktivorous fish ("herring") (Nøst et al., 2013). Individual dietary input information was derived from the questionnaire responses and is described in detail in Supplemental Material, pp. 2–3 and summarised in Table 1. Body weight and lipid mass in the women was not described by person-specific information but by the default parameterization.

To evaluate the importance of person-specific input for the predictive ability of CoZMoMAN we performed additional simulations for PCB-153 where individual input values were replaced with median or fixed values for all individuals (described in Supplemental Material, pp. 7-8).

Table 1: Summary of input information to CoZMoMAN simulation of MISA (*n*= 310) and NOWAC (*n*= 244) women.

	MISA			NOWAC		
Variable	Median	Min	Max	Median	Min	Max
Birth year	1977	1965	1991	1949	1943	1957
Number of children	1	0	4	2	0	4[a]
Age at 1st child	26	-	41	23	-	39
Age at 2nd child	28	-	37	27	-	40
Age at 3rd child	30	-	36	30	-	38
Age at 4th child	32	-	33	32	-	41
Months of breastfeeding of 1st child	12	-	36	4	-	36
Months of breastfeeding of 2nd child	12	-	38	5	-	26
Months of breastfeeding of 3rd child	13	-	22	6	-	36
Months of breastfeeding of 4th child	15	-	30	6	-	30
Daily intake of fish (g fresh weight/day)	51.2	3.29	137	75.4	0.86	199
Daily intake of dairy products (g lipid/day)	11.1	2.02	44.8	12.0	0.99	70.7
Daily intake of meat (g lipid/day)	16.2	2.83	34.9	15.0	1.52	33.7

2.4. Data treatment and statistical methods

Statistical analyses were done with R, ver.3.0.0, and statistical significance was defined as $p < 0.05$. Almost all PCB concentrations had lognormal distributions as evaluated by Shapiro-Wilk tests. For the presented MISA results, summary statistics for compounds with detection frequencies between 20% and 80% were performed with maximum likelihood estimation in the NADA package for R (Helsel, 2005).

The numbers of individuals included in the evaluation of CoZMoMAN-predicted and measured concentrations of PCB-153 were 310 and 244 from the MISA and NOWAC study, respectively. We excluded individuals who had incomplete information sets (questionnaire, PCB measurement and details of child births) and individuals with a diet not typical for the model domain or consuming food items that are known to be heavily contaminated (e.g. seagull eggs) yet are not considered by CoZMoMAN (see Supplemental Material, pp. 4).

Predicted and measured concentrations were compared in scatter plots, a variant of Bland-Altman plots and by Spearman`s $r_s$ rank correlation values. Further, measured and predicted values were divided into quartiles and the weighted Cohen`s κ, as a measure of inter-method agreement in categorical sorting, was subsequently calculated for the quartile categorization. In order to evaluate systematic discrepancies (individual concentration deviations) between measurements and CoZMoMAN predictions, we assessed potential relationships between discrepancies and input parameters as well as dietary and lifestyle variables not accommodated by CoZMoMAN.

A statistical approach employing linear regression models served to evaluate the individualised input parameters and identify potential influential predictors not accommodated by CoZMoMAN. Both model input parameters and individual food items from questionnaires were assessed in this way. Regression models were constructed separately for MISA and NOWAC women and predicted individual concentrations were derived from the best fitted models (see detailed description in Supplemental Material, pp. 9-10). Further, the agreement between these predictions and measurements was evaluated in the same way as for the CoZMoMAN predictions.

3. Results

3.1. Concentrations of PCBs 118, 138, 153 and 180 in Norwegian women

Summary statistics of concentrations of four PCBs in serum of pregnant women from Northern Norway are presented in Table 2 (wet weight concentrations and limits of detection are presented in Table S1). These concentrations were similar to those previously reported in a subgroup of the women (*n*= 50) (Hansen et al., 2010). Concentrations of the same PCBs in plasma from postmenopausal Norwegian women were reported by Rylander et al. (2012) and median (range) concentrations of PCBs 118, 138/163, 153, and 180 were 14 (<LOD-49), 62 (<LOD-164), 82 (<LOD-211), 65 (<LOD-182) ng/g lipid weight, respectively.

Table 2: Concentrations (ng/g, lipid weight) of PCBs[a] in serum of pregnant women in Northern Norway. Sampling took place in the second trimester of pregnancies during 2007-2009.

Compound	AM[b]	SD[c]	Median	Range	*n*[d]	% >LOD[e]
PCB-118	4.7	3.2	4.0	<LOD - 38	513	97
PCB-138	16	10	14	2.1 - 118	513	100
PCB-153	28	17	24	3.3 - 201	507	100
PCB-180	18	12	16	3.0 - 158	513	100

[a]Censored summary statistics are presented for compounds with detection frequencies less than 80%.
[b]AM = Arithmetic mean
[c]SD = Standard deviation
[d]*n*= Number of samples analysed and quantified
[e]% > LOD = Percentage of samples in which analyte was detected.

3.2. The ability of CoZMoMAN to predict person-specific concentrations

Comparisons of concentrations predicted by CoZMoMAN with those measured in MISA and NOWAC women are displayed for PCB-153 in Figure 1 and Table 3, and for PCBs 118, 138, and 180 in Supplemental Material, Figure S1 and Table S2.

Table 3: The median predicted concentrations of PCB-153 (ng/g lipid) and their median discrepancy from measurements along with the ratio and rank correlation between predicted and measured concentrations.

Study group	Median prediction	Median discrepancy	Median ratio (range)	Correlation r_s	Correlation p
MISA	28.8	+4.8	1.06 (0.16-6.44)	0.40	p<0.0001
NOWAC	78.2	-3.3	0.94 (0.16-7.92)	0.13	p<0.0001
Both combined	-	-	-	0.67	p=0.001

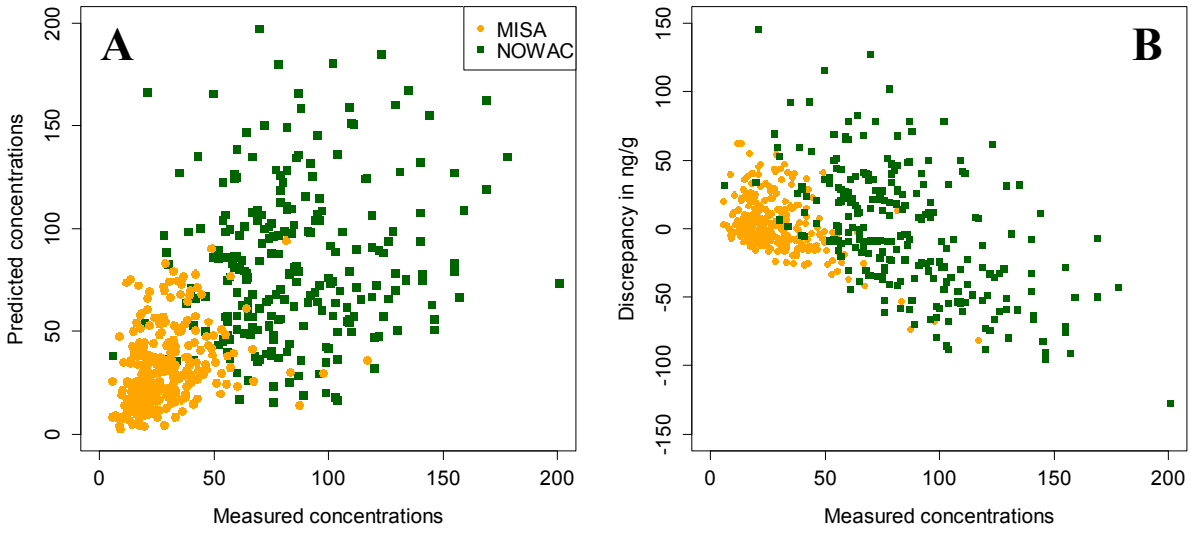

Figure 1: Measured serum concentrations of PCB-153 along with those predicted (both in ng/g lipid) by CoZMoMAN for the MISA (orange dots, *n*=310) and NOWAC (green squares, *n*=244) study subjects (A). Discrepancies between the measured and predicted concentrations are displayed according to the measured concentrations in the two study groups (B).

3.3. Evaluation of CoZMoMAN input parameters

Predictors influencing the discrepancies of predicted and measured concentrations are evaluated in Supplemental Material, Figure S2, Table S3 and S4. The estimated daily fish intakes explained the most variance in discrepancies of CoZMoMAN predictions (Supplemental Material, Figure S2 and Table S3). Indeed, fish intake, birth year and duration of breastfeeding were associated with discrepancies (Supplemental Material, Table S3). The correlation between measured and predicted concentrations was better for women with children (r_s=0.67, p<0.0001. *n*= 157 MISA women and 234 NOWAC women) as compared to women without children (r_s=0.44, p<0.0001, *n*=156 MISA women and 10 NOWAC women). Replacing individual values with median daily intakes of meat, fish and dairy products increased correlation from that observed when individual information was used for MISA women; however, this resulted in unrealistically narrow predictions for NOWAC women (Supplemental Material, Figure S3). The correlation in all other hypothetical simulations decreased correlation to the measured concentrations (Supplemental Material, Table S4).

3.4. Predictions of PCB-153 concentrations from linear regression models

Linear regression models including variables that were used as CoZMoMAN input information (Table 1) explained 67% of variation overall and 28% and 21% for MISA and NOWAC women separately (not presented). Extended models including any significant covariates from questionnaire information were also evaluated. The included covariates in the best fitted models differed between MISA and NOWAC women (Supplemental Material, pp. 9-10). Birth year and duration of breastfeeding were significant predictors for both study groups. Additionally, body weight and intake of fish liver and freshwater fish were significant predictors for MISA women. Predictions derived from these models correlated with measurements with r_s=0.65, p<0.0001 for the MISA women and r_s=0.52, p<0.0001 for the NOWAC women (Figure 2). Furthermore, median predicted concentrations agreed well with the measured ones: median 27.1 and 24.3 ng/g lipid, respectively (factor ranging 0.13-4.34), for MISA women, and 85.4 and 80.5 ng/g lipid, respectively (factor ranging 0.21-5.25), for NOWAC women.

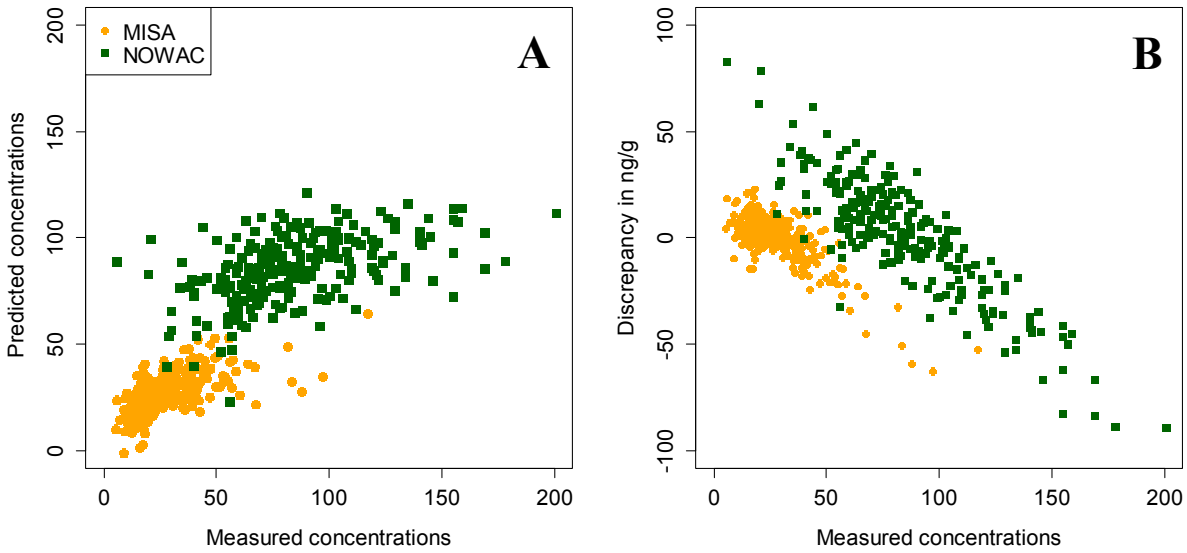

Figure 2: Measured serum concentrations of PCB-153 along with those predicted (both in ng/g lipid) from statistical linear regression models for MISA (orange dots, *n*=310) and NOWAC (green squares, *n*=233) study subjects (A). Discrepancies between the measured and predicted concentrations are displayed according to the measured concentrations in the two study groups (B).

3.5. The ability of CoZMoMAN to predict quartile classification

Table 4 gives the number of individuals assigned to the correct quartile based on both CoZMoMAN predictions and regression analyses as well as the weighted Cohen`s κ as measure of agreement in quartile categorization from measurements and predictions.

Table 4: Agreement in quartile categorization based on predictions obtained from CoZMoMAN and linear regressions compared to the measured concentrations in MISA and NOWAC women.

Approach	Correct quartile n (%)			Weighted Cohen`s κ		
	MISA	**NOWAC**	**Combined**	**MISA**	**NOWAC**	**Combined**
Mechanistic modelling	120/309 (39%)	63/244 (26%)	251/553 (48%)	0.38	0.12	0.64
Linear regression models	142/308 (46%)	91/232 (39%)	341/540 (63%)	0.59	0.46	0.81

3.6. Individual LBATs

The CoZMoMAN generated estimates of LBATs varied significantly between individuals. Figure 3A illustrates this predicted variability by plotting concentrations obtained from CoZMoMAN from birth until 2010 for a few selected MISA (n=4) and NOWAC (n=4) women along with their measured concentrations at the time of sampling. These women were chosen to represent different birth years and number of children. In all individuals, predicted concentrations at different ages and cumulative exposures during puberty (represented by the area-under-the-curve (AUC) for concentrations from 11 to 16 years of age) were derived and are presented in Figure 3B-3E. Age at first child birth was considered 23 and 26 years for MISA and NOWAC women, respectively. Rank correlations between the predictions of past concentrations and measured and predicted concentrations at the sampling time are presented in Table 5.

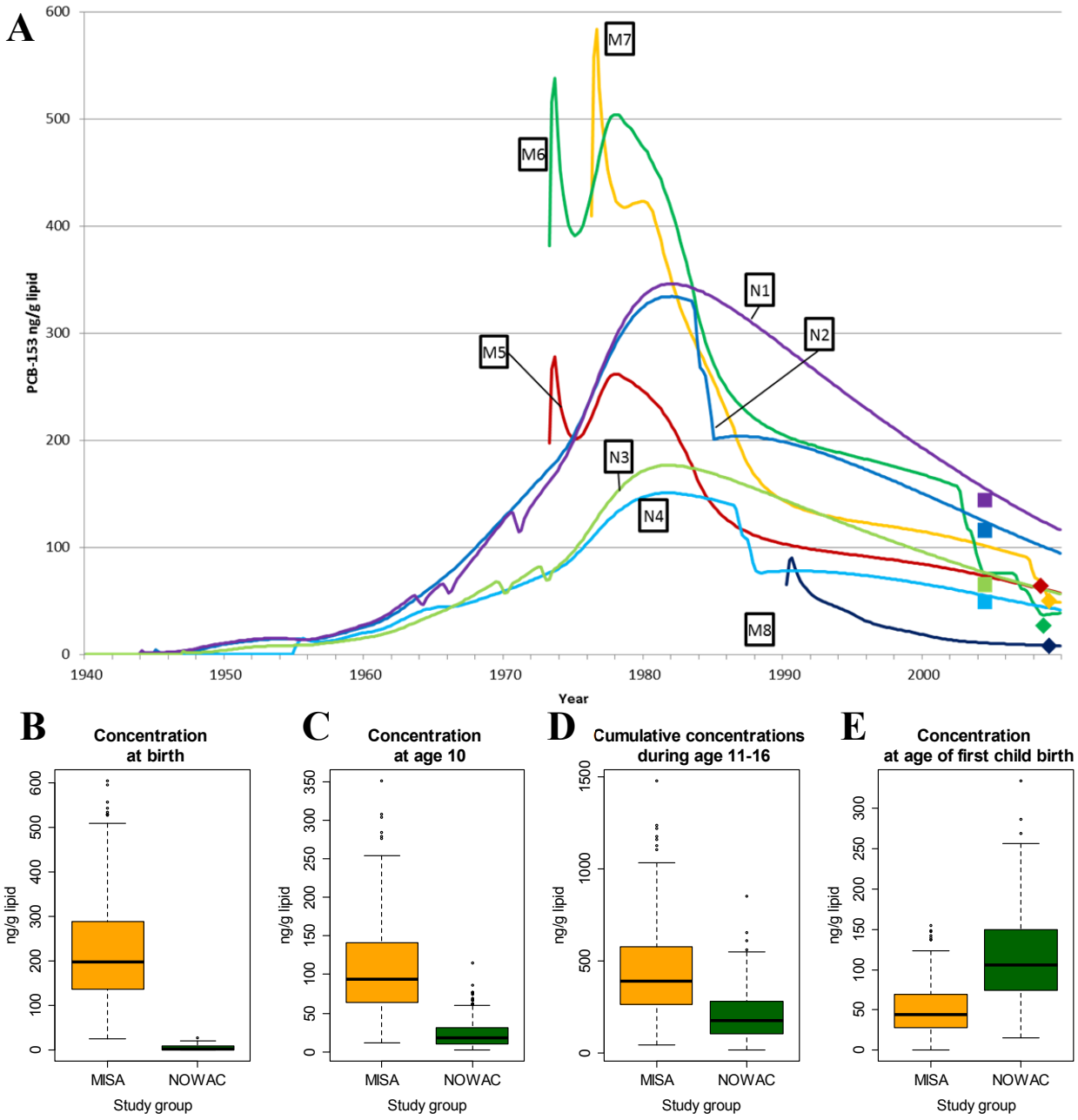

Figure 3: A) Predicted concentrations of PCB-153 for four MISA and four NOWAC women from their birth until 2010 are displayed along with the concentrations measured at the time of sampling for each woman. MISA women (N, diamond shaped marker point) were sampled in 2007-2009 and NOWAC women (M, square shaped marker point) were sampled in 2004. N1: born in 1944, children born in 1963, 1965, and 1970; N2: born in 1945, child born in 1984; N3: born in 1947, children born in 1970 and 1973; N4: born in 1955, children born in 1987 and 1988; M5: born in 1973, no children; M6: born in 1973, children born in 2003 and 2007; M7: born in 1976, child born in 2008; M8: born in 1990, no children. Person-specific predictions of

concentrations at birth (B), at 10 years of age (C), of cumulative concentrations during puberty (age 11-16 years) (D), and of concentrations at age of first child birth (E) are displayed separately for the two study groups.

Table 5: Rank correlation r_s between person-specific predictions of concentrations experienced in the past and at sampling time with the measured concentrations. The number of included women was 310 and 233 from the MISA and NOWAC studies, respectively.

Predictions of concentrations	**Prediction at time of measurement**		**Measurement**	
	MISA	**NOWAC**	**MISA**	**NOWAC**
At birth	0.68	0.27	0.05[a]	-0.32
At 1 year	0.69	0.23	0.06[a]	-0.33
At 10 years	0.65	0.39	0.29	-0.31
During puberty	0.66	0.44	0.29	-0.29
At age of first child birth	0.60	0.72	0.38	-0.13

[a]Correlation was not significant

4. Discussion

4.1. Concentrations in Norwegian pregnant and postmenopausal women

The median PCB-153 concentrations in the postmenopausal NOWAC women (Rylander et al., 2012) were roughly three times higher than those in the pregnant MISA women (Table 2). The median age was 29 years older in NOWAC women compared to MISA women. Higher concentrations in older individuals are expected because of the birth cohort effect, i.e. the body burden in older women is a remnant of much higher PCB exposure they had experienced in the past (Nøst et al., 2013; Quinn and Wania, 2012). Different dietary habits between the two study groups could also contribute to the observed differences (Quinn et al., 2012). Indeed, while consumption of marine food items was a predictor of PCBs in NOWAC women (Rylander et al., 2012), MISA women reported to consume less fish compared to the NOWAC women; however, daily intakes of many food items (including fish roe and liver) were comparable between the groups. Parity was generally higher in NOWAC women as compared to MISA women (17 and 212 nulliparous women, respectively), and thus concentrations of PCBs in NOWAC women could have been even higher when considering the loss of PCBs during pregnancy and breastfeeding (Norén and Meironyté, 2000; Thomsen et al., 2010). Time of sample collection in the MISA and NOWAC studies was 2007-2009 and 2004, respectively, and the influence of decreasing time trends of PCBs in humans during these years on the concentration differences between subject groups is likely modest.

4.2.Predictive ability of CoZMoMAN on group level

The median predicted PCB-153 concentrations in MISA and NOWAC women were within 20% and 4%, respectively, of the measured ones. The predicted concentrations were in good agreement with those measured for PCBs 153 and 180 whereas they were slightly too high for PCB-118 in both study groups and slightly too low for PCB-138 in NOWAC women. The latter may be due to the co-elution of PCB-138 and 163 in analyses of the NOWAC samples (quantified separately in MISA samples). For PCB-118, similar small model discrepancies have

been observed in previous model evaluations (Czub and McLachlan, 2004; Nøst et al., 2013) and likely reflect inaccurate estimates of its metabolic degradation half-lives (Czub and McLachlan, 2004). A study of group level CoZMoMAN predictions in elderly men from Northern Norway also indicated good agreement between predicted and measured median PCB-153 concentrations for five serum measurements between 1979 and 2007 (Nøst et al., 2013). Also, the predicted time trends fit well. Together, these results lend strong support for the accuracy of the emission estimates and the quantitative description of environmental fate and human bioaccumulation, especially for PCBs 153 and 180.

4.3. Person-specific predictions of PCB-153 using CoZMoMAN

The rank correlation of measured concentrations of PCB-153 and CoZMoMAN predictions was strong (r_s=0.67) for both groups combined; however, that correlation was weaker when both groups were ranked separately and better for the MISA women (r_s=0.40) as compared to the NOWAC women (r_s=0.13). The ranges of PCB-153 concentrations generated by CoZMoMAN for the MISA and NOWAC women were very similar to the measured ones and demonstrate that CoZMoMAN is able to reproduce realistic concentrations in women of different ages and parity. Notably, a perfect fit was not expected as the model assumes homogeneous background exposure through food chain-related intake to all individuals and does not incorporate spatial (discriminating high and low contaminated environments in Norway with regards to e.g. PCB-content in fish (Nilsen et al. 2011; Skåre et al. 2008)) nor individual variation in all model parameters (such as metabolism or BMI).

The stronger correlations of measured and predicted concentrations for MISA women compared to NOWAC women could be related to the fact that the former originate from Northern Norway whereas the latter from all of Norway. The CoZMoMAN predictions for the PCB content in fish may be more representative for Northern Norway. The predictive ability of CoZMoMAN was best for the lowest concentrations and predictions underestimated the highest measured concentrations (Figure 1); however, relative discrepancies were lower for the higher concentrations. The prediction errors were largely explained by birth year, total breastfeeding and daily intakes of fish (along with body weight for MISA women; Supplemental Material, Table

S3). Disregarding person-specific dietary intakes in simulations increased the correlation of predictions and measurements for MISA women whereas this assumption led to an unrealistically small range of concentrations for NOWAC women (Supplemental Material, Figure S3). The variability in the concentrations predicted for the NOWAC women is largely due to the variable intake of fish (Supplemental Material, Figure S2). However, the measured concentrations show much less relationship with fish intake (Supplemental Material, Figure S2), although the range of measured and predicted concentrations is similar. This suggests that factors other than fish intake are responsible for the variability in the concentrations of NOWAC women; factors that are presently not considered by CoZMoMAN. It is unlikely that flawed food frequency questionnaires in the study groups are responsible for the failure of CoZMoMAN to accurately capture the inter-individual differences between these women, because they are considered of good quality and calculated dietary intake estimations realistic (Rylander et al., 2012; Totland et al., 2012; Veyhe et al., 2012). Some variation in discrepancies of predicted concentrations was associated with the breastfeeding variable; however, correlations to measured concentrations were better for women who had children than for nulliparous women.

Accounting for individual differences in parameters regarded as fixed by CoZMoMAN, such as body weight, could have improved model performance. Lipid-normalised concentrations depend on the body lipid stores and temporal changes in body lipid compartments have been suggested to influence the human half-lives of DDT (Wolff et al., 2007). Thus, the observed association between discrepancies of predicted concentrations and reported body weights could indicate that this factor should be individually parameterised in CoZMoMAN. Another contributing factor to individual variation in concentrations could be varying metabolic capacities of PCBs (Shirai and Kissel, 1996; Wolff et al., 1992) which CoZMoMAN is sensitive to (Quinn and Wania, 2012) although its individual parameterisation is not feasible.

4.4. Person-specific predictions of PCB-153 using statistical linear regressions

Regression models were intended to identify predictors not accounted for by CoZMoMAN and the best fitted regression models of PCB concentrations included the following predictors: i) birth year and duration of breastfeeding for both study groups; ii) body weight, intake of fish liver and

freshwater fish for MISA women (Supplemental Material, Table S5). These predictors accounted for 36% and 22% of variation in concentrations in MISA and NOWAC women, respectively. Multivariate analyses in MISA women indicated age, parity, BMI and dietary intakes of freshwater fish, fat fish, fish liver and reindeer as significant predictors (Anna Sofia Veyhe, personal communication). MISA women who consumed seagull eggs were disregarded in the evaluation of the performance of CoZMoMAN as this exposure route is not accounted for by the model; however, it was an important predictor in these women (Supplemental Material, Table S5) and also in a large cohort of pregnant Norwegian women (Caspersen et al., 2013). Intake of marine food has been identified as predictors of PCB concentrations in NOWAC women employing a multivariate approach (Rylander et al., 2012); however, total intake of fish was borderline significant for the NOWAC women.

4.5. Summary of person-specific PCB predictions

Evaluation of predictions suggest that a priori estimates of person-specific PCB concentrations from CoZMoMAN based on questionnaire-based information could represent valuable supplements to single measurements in exposure characterization. Predictions and measurements could be compared here for a large sample set that included questionnaire data of good quality. Both CoZMoMAN simulations and regression analyses provided good rank correlations and individual quartile categorization that agreed well with those of measured concentrations (weighted Cohen`s $\kappa>0.6$) when MISA and NOWAC women were regarded collectively. Correlation was weaker when each study group was regarded separately demonstrating that rank correlations are better when the study population is heterogeneous (e.g. includes older and younger persons).

The main predictors of PCB concentrations indicated by statistical approaches were accounted for by CoZMoMAN. Additionally, results suggested that individual parameterisation of body weight and intakes of heavily contaminated food items such as seagull eggs by CoZMoMAN could have improved predictions of concentrations in these women. Agreement between measured and predicted concentrations was better for predictions from regression models compared to from CoZMoMAN; however, this was expected as regression models are

constructed from measurements and variation therein. Also, there is no mechanistic significance of their predictors.

Person-specific predicted PCB concentrations have previously been attempted and the predictive ability of regression approaches in this study was similar to that in a Norwegian subpopulation with high intakes of fish and game (Kvalem et al., 2012) and in elderly women in Sweden (Bergkvist et al., 2012). Capability of reproducing individual PCB measurements from CoZMoMAN was similar to that from: i) a pharmacokinetic model based on dietary intake rates for Greenlandic Inuit adults (Sonne et al., 2014); and ii), a toxicokinetic model predicting three measurements throughout early childhood (Verner et al. 2013). Taken together, precision of the mechanistic calculations of person-specific PCB concentrations from emission estimates are comparable to those of other approaches.

4.6. Single measurements and predicted LBATs

The time-resolved feature of CoZMoMAN allows for an expanded understanding of individual exposures with regards to predicting LBATs. Figure 3 clearly shows the large individual differences in LBATs and concentrations at different ages in study subjects and that single measurements alone do not reveal the inter-individual differences in past exposure. Evidently, the conceptual understanding of variation and influential predictors as well as estimates of past concentrations are relevant for characterization of PCB exposures. Thus, such estimates may complement single measurements and provide useful information for effect-related studies. Indeed, point estimates of concentrations at birth, 10 years of age and at average age of first child birth along with an estimate of cumulative exposure during puberty (11-16 years of age) were derived for the MISA and the NOWAC women. The rank correlation between predicted individual concentrations at the time of sampling correlated strongly with the concentrations predicted earlier in life for MISA women (Table 5). For NOWAC women, corresponding correlations increased from birth until age of first child birth, i.e. with decreasing time between sampling and the assumed period of exposure susceptibility. However, measured concentration at the time of sampling appears to be only weakly correlated to the exposure predicted for possible time periods of high susceptibility earlier in life. Although temporal changes of concentrations

cannot be evaluated on the basis of observations presented herein, key features of observed human temporal trends of PCBs have been reproduced by CoZMoMAN (Breivik et al., 2010; Nøst et al., 2013). Our results using CoZMoMAN nevertheless confirm the potential of estimations of past individual exposures as exposure metrics in epidemiological studies, previously suggested by Bachelet et al. (2010) and Verner et al. (2011).

In the individual LBATs presented in this study, it is evident that the highest concentrations in NOWAC women occurred when they were adults whereas MISA women experienced peak exposures at birth. Breastfeeding of children by NOWAC women had little impact on their LBATs when it occurred before the early 1980s (N1 and N3) whereas breastfeeding in the 1980s caused concentrations in those older mothers to drop significantly (N2 and N4). Breastfeeding also lowered concentrations in MISA women (M6 and M7) and changed the individual ranking of PCB burdens at the time of sampling in MISA women (M6 and M7 relative to M5). The influence of reproductive behaviour on PCB-153 concentrations in mothers and their children according to the CoZMoMAN model is thoroughly discussed by Quinn et al. (2011).

4.7. Conclusions

The CoZMoMAN model was able to predict group medians and ranges of PCB concentrations in pregnant and postmenopausal Norwegian women with high precision. Furthermore, ranking of individuals based on predictions and measurements were largely consistent, although weaker when both study groups were regarded separately. Although the statistical analysis designates fish intake as a predictor of PCB concentrations, CoZMoMAN attributes too much of the inter-individual differences to variable fish intake. Statistical approaches identified concentrations predictors not explicitly addressed in CoZMoMAN. Predicted LBATs derived from CoZMoMAN suggested large differences in past concentrations experienced by the MISA and NOWAC women.

Mechanistic modelling provides information of individual concentrations through life that are valuable and useful supplements to exposure characterization in cross-sectional PCB measurements.

Acknowledgements

The project was financially supported by the Northern Norway Regional Health Authority with additional funding provided by the Research Council of Norway (KB). We are grateful to the study participants. We thank Solrunn Hansen, Anna Sofia Veyhe, Guri Skeie, Nicolle Mode and Eilif Lund for access to the databases of information in the MISA and NOWAC cohorts. The authors declare they have no competing financial interests.

5. References

Akins, JR, Waldrep, K, Bernert Jr, JT. 1989. The estimation of total serum lipids by a completely enzymatic 'summation' method. Clin Chim Acta 184(3):219-226.

Alcock RE, Sweetman AJ, Juan CY, Jones KC. 2000. A generic model of human lifetime exposure to persistent organic contaminants: Development and application to PCB-101. Environ Pollut 110(2):253-265.

Bachelet D, Verner M-A, Guihenneuc-Jouyaux C, Charlier C, Charbonneau M, Haddad S, et al. 2010. Assessment of exposure to persistent organochlorine compounds in epidemiological studies on breast cancer: a literature review and perspectives for the CECILE study. Acta Clinica Belgica 65(supplement1): 49-57.

Bergkvist, C, Åkesson, A, Glynn, A, Michaëlsson, K, Rantakokko, P, Kiviranta, H, Wolk, A, Berglund, M. 2012. Validation of questionnaire-based long-term dietary exposure to polychlorinated biphenyls using biomarkers. Mol Nutr Food Res 56(11):1748-1754.

Binnington, MJ, Quinn, CL, McLachlan, MS, Wania, F. 2014. Evaluating the effectiveness of fish consumption advisories: Modeling prenatal, postnatal, and childhood exposures to persistent organic pollutants. Environ Health Perspect 122(2):178-186.

Breivik, K, Czub, G, McLachlan, MS, Wania, F. 2010. Towards an understanding of the link between environmental emissions and human body burdens of PCBs using CoZMoMAN. Environ Int 36(1):85-91.

Caspersen, IH, Knutsen, HK, Brantsæter, AL, Haugen, M, Alexander, J, Meltzer, HM, Kvalem, HE. 2013. Dietary exposure to dioxins and PCBs in a large cohort of pregnant women: Results from the Norwegian mother and child cohort study (MoBa). Environ Int 59:398-407.

Czub, G, McLachlan, MS. 2004. A food chain model to predict the levels of lipophilic organic contaminants in humans. Environ Toxicol Chem 23(10):2356-2366.

Darnerud, PO, Atuma, S, Aune, M, Bjerselius, R, Glynn, A, Grawé, KP, Becker, W. 2006. Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on Swedish market basket data. Food Chem Toxicol 44(9):1597-1606.

Hansen, S, Nieboer, E, Odland, JØ, Wilsgaard, T, Veyhe, AS, Sandanger, TM. 2010. Levels of organochlorines and lipids across pregnancy, delivery and postpartum periods in women from Northern Norway. J Environ Monit 12:2128-2137.

Helsel, RD. 2005. Nondetects and data analysis. Statistics for censored environmental data. Hoboken, NJ:Wiley Interscience.

Kvalem, HE, Brantsæter, AL, Meltzer, HM, Stigum, H, Thomsen, C, Haugen, M, Alexander, J, Knutsen, HK. 2012. Development and validation of prediction models for blood concentrations of dioxins and PCBs using dietary intakes. Environ Int 50:15-21.

Moser GA, McLachlan MS. 2002. Modeling digestive tract absorption and desorption of lipophilic organic contaminants in humans. Environ Sci Technol 36(15):3318-3325.

Nilsen BM, Frantzen S, Julshamn K. 2011. Fremmedstoffer i villfisk med vekt på kystnære farvann 2009 [in Norwegian]. Bergen, Norway. National Institute of Nutrition and Seafood Research Report. Available: http://www.nifes.no/file.php?id=1311 [accessed 28 March 2014].

Norén, K, Meironyté, D. 2000. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. Chemosphere 40(9-11):1111-1123.

Nøst, TH, Breivik, K, Fuskevåg, O-M, Nieboer, E, Odland, JØ, Sandanger, TM. 2013. Persistent organic pollutants in Norwegian men from 1979 to 2007: Intraindividual changes, age–period–cohort effects, and model predictions. Environ Health Perspect 121(11-12):1292–1298.

Quinn, CL, Armitage, JM, Breivik, K, Wania, F. 2012. A methodology for evaluating the influence of diets and intergenerational dietary transitions on historic and future human exposure to persistent organic pollutants in the Arctic. Environ Int 49:83-91.

Quinn, CL, Wania, F. 2012. Understanding differences in the body burden-age relationships of bioaccumulating contaminants based on population cross-sections versus individuals. Environ Health Perspect 120(4):554-559.

Quinn, CL, Wania, F, Czub, G, Breivik, K. 2011. Investigating intergenerational differences in human PCB exposure due to variable emissions and reproductive behaviors. Environ Health Perspect 119(5):641-646.

Ritter R, Scheringer M, MacLeod M, Schenker U, Hungerbühler K. 2009. A multi-individual pharmacokinetic model framework for interpreting time trends of persistent chemicals in human populations: Application to a postban situation. Environ Health Perspect 117(8):1280-1286.

Rylander, C, Lund, E, Frøyland, L, Sandanger, TM. 2012. Predictors of PCP, OH-PCBs, PCBs and chlorinated pesticides in a general female Norwegian population. Environ Int 43:13-20.

Shirai, JH, Kissel, JC. 1996. Uncertainty in estimated half-lives of PCBs in humans: Impact on exposure assessment. Sci Total Environ 187(3):199-210.

Skåre JU, Alexander J, Arukwe A, Eggen T, Eriksen GS, Fæste CK, et al. Opinion of the Panel on Contaminants of the Norwegian Scientific Committee for Food Safety. Risk assessment of non dioxin-like PCBs in Norwegian food. Available: http://www.vkm.no/dav/c29e178d9c.pdf [accessed 23 March 2014].

Skeie, G, Hjartåker, A, Lund, E. 2006. Diet among breast cancer survivors and healthy women. The Norwegian women and cancer study. Eur J Clin Nutr 60(9):1046-1054.

Sonne, C, Gustavson, K, Rigét, FF, Dietz, R, Krüger, T, Bonefeld-Jørgensen, EC. 2014. Physiologically based pharmacokinetic modeling of POPs in Greenlanders. Environ Int 64:91-97.

Thomsen, C, Haug, LS, Stigum, H, Frøshaug, M, Broadwell, SL, Becher, G. 2010. Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. Environ Sci Technol 44(24):9550-9556.

Totland, TH, Melnæs, BK, Lundberg-Hallén, N, Helland-Kigen, KM, Lund-Blix, NA, Myhre, JB, et al. 2012. Norkost 3. En landsomfattende kostholdsundersøkelse blant menn og kvinner i Norge i alderen 18-70 år, 2010-2011 [in Norwegian]. Oslo, Norway: Norwegian Directorate of Health. Available: http://www.helsedirektoratet.no/publikasjoner/norkost-3-en-landsomfattende-kostholdsundersokelse-blant-menn-og-kvinner-i-norge-i-alderen-18-70-ar/Publikasjoner/norkost-3-is-2000.pdf [accessed 30 January 2014].

Verner M-A, Sonneborn D, Lancz K, Muckle G, Ayotte P, Dewailly É, et al. 2013. Toxicokinetic modeling of persistent organic pollutant levels in blood from birth to 45 months of age in longitudinal birth cohort studies. Environ Health Perspect 121(1):131-137.

Verner M-A, Bachelet D, McDougall R, Charbonneau M, Guénel P, Haddad S. 2011. A Case Study Addressing the Reliability of Polychlorinated Biphenyl Levels Measured at the Time of Breast Cancer Diagnosis in Representing Early-Life Exposure. Cancer Epidemiology Biomarkers & Prevention 20(2): 281-286.

Verner MA, Charbonneau M, López-Carrillo L, Haddad S. 2008. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environ Health Perspect 116(7):886-892.

Veyhe, AS, Hansen, S, Sandanger, TM, Nieboer, E, Odland, JØ. 2012. The Northern Norway mother-and-child contaminant cohort study: Implementation, population characteristics and summary of dietary findings. Int J Circumpolar Health 71.

Waaseth, M, Bakken, K, Dumeaux, V, Olsen, KS, Rylander, C, Figenschau, Y, et al. 2008. Hormone replacement therapy use and plasma levels of sex hormones in the Norwegian women and cancer postgenome cohort–a cross-sectional analysis. BMC Womens Health 8(1):1.

Wolff, MS, Anderson, HA, Britton, JA, Rothman, N. 2007. Pharmacokinetic variability and modern epidemiology—the example of dichlorodiphenyltrichloroethane, body mass index, and birth cohort. Cancer Epidemiol Biomarkers Prev 16(10):1925-1930.

Wolff, MS, Fischbein, A, Selikoff, IJ. 1992. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res 59(1):202-216.

SUPPLEMENTAL MATERIAL

Person-specific predictions of PCBs in Norwegian Women: Valuable supplements to measurements for understanding of time-variant exposures

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Supplemental Material, Detailed information on parameters in CoZMoMAN

The original model domain includes Sweden and parts of Southeastern Norway (Breivik et al., 2010) and the current simulations relied upon exactly the same model parameterization, except for input parameters reflecting individual subjects. The input parameters specified for each subject were birth date and year, number of children, age at childbirth(s), duration of breastfeeding of each child, and four dietary variables. Only birth year was available for NOWAC women and Jan 1st was assumed date of birth for these women. Body weight was available in questionnaire information but was assumed constant between individuals as it could not be accounted for in the model. Metabolic rate is also assumed constant between individuals by CoZMoMAN. The model assumes age-dependent changes in body weight and lipid weight whereas the human metabolic rate is assumed to be constant across ages and between individuals. The model was run from 1930 to 2010 with 1 hour resolution for the PCB-153 simulations, whereas with 12 hour resolution for the other PCB congeners and for hypothetical evaluative simulations. Results from simulations ran with resolution of both 1 and 12 hours differed less than one percent.

- Dietary input information

The dietary information that could be incorporated into the model for each individual was daily intakes of fish (grams, wet weight), meat (grams, lipid weight) and dairy products (grams, lipid weight) in addition to a ratio of piscivorous and planktivorous fish to represent the trophic level of the fish consumed. The original description of dietary habits is based on the general food consumption of the Swedish population (Czub and McLachlan 2004); however, in this study individual daily intakes of food items were derived from food frequency questionnaires. Calculated dietary intakes of individual food items were classified as fish, meat or dairy and summed accordingly. Contributions from mixed products were estimated from percentages of fish, meat or dairy (e.g. fish in fish cakes roughly estimated from available information on common brands). The summed intakes were similar to those described for the study groups in Veyhe et al. (2012) and Rylander et al. (2012). The lipid content of meat and dairy food items were obtained from the Norwegian Food Composition Table (Norwegian Food Safety Authority). CoZMoMAN assumes 0.5% lipid in fish which is the lipid content of fish muscle (Czub and

McLachlan, 2004) and due to the high lipid content in fish liver, wet weight daily intakes of this food item were multiplied by a factor of 50 (Norwegian National Institute of Nutrition and Seafood Research). The food frequency questionnaire did not cover many different piscivorous and planktivorous fish and hence a calculated ratio of fish from different trophic levels for each individual was not representative. Rather, the percentage of piscivorous and planktivorous fish represented by "herring" and "cod" was assumed 35% and 65%, respectively, for all women. This assumption was considered appropriate in past CoZMoMAN simulations for men from Northern Norway (Nøst et al., 2013).

Daily dietary intakes were estimated from food frequency questionnaires answered at the time of blood sampling (asking for consumption of many different food groups during the preceding year) and dietary habits are assumed equal throughout the entire life of the woman. An age-dependent ingestion rate, $I_{default}(X)$, is assumed within CoZMoMAN (Equation 1) and the input intake at 25 years, $I_{individual}(25)$, was specified as model input (Czub and McLachlan, 2004). The estimated dietary intake rates for an individual at time of blood sampling at age X, $I_{individual}(X)$, was adjusted according to Equation 2 to represent the intake rates at age 25 $I_{individual}(25)$:

$$I_{default}(X)\ (\text{g dry weight/h}) = (0.0000007044 * Age^5 - 0.00020058 * Age^4 + 0.022579 * Age^3 - 1.346 * Age^2 + 39.322 * Age + 46.199) / 24 \quad \text{(Equation 1)}$$

$$I_{individual}(25) = I_{default}(25)\ x\ I_{individual}(X)/I_{default}(X) \quad \text{(Equation 2)}$$

- Input information of breastfeeding

Information of total months of breastfeeding (representing both exclusive and partial breastfeeding) for each child was available in both study groups and used to represent duration of breastfeeding as input information for the presented simulations.

For MISA women, information on months of exclusive and partial breastfeeding was available from questionnaires. Additional simulations parameterized with exclusive (months of solely breast milk fed to the infant) or partial breastfeeding (months of solely breastfeeding with an addition of half the months infants was fed breast milk and regular food) were performed; however, predicted concentrations were underestimated and correlated less strongly with observations (data not shown).

Supplemental Material, Inclusion criteria for evaluated predictions

Concentration of PCB-153 was determined for 507 and 269 women in the MISA and NOWAC study group, respectively. Evaluation of CoZMoMAN predictive ability was restricted to persons for which individual parameterisation was possible. Furthermore, CoZMoMAN is parameterized for the western part of the Baltic Sea drainage basin (which includes Sweden and parts of Norway) and assumes dietary exposure through fish, meat and dairy products. Persons with incomplete questionnaire information for any variable used as model parameterisation (*n*= 116) were excluded. Additionally, individuals who stated to "not eat Norwegian diet on a regular basis" (*n*= 39), to consume seagull eggs (MISA women, *n*= 59) or to have more than five children (*n*= 8) were excluded. Hence, the total numbers of individuals included in these evaluations were 310 and 244 in MISA and NOWAC study groups, respectively.

Supplemental Material, Table S1: Concentrations (pg/g, wet weight) of PCBs[a] in serum of pregnant women in Northern Norway.

Compound	AM[b]	SD[c]	Median	Range	*n*[d]	% >LOD[e]	LOD
PCB-118	31.0	20.5	26.1	<LOD - 227	513	97	10
PCB-138	110	69.4	95.1	15.8 - 860	513	100	13
PCB-153	183	119	159	25.5 - 1470	507	100	14
PCB-180	123	84.1	105	16.8 - 1160	513	100	15

[a]Censored summary statistics are presented for compounds with detection frequencies less than 80%.
[b]AM = Arithmetic mean
[c]SD = Standard deviation
[d]*n* = Number of samples analysed and quantified
[e]% > LOD = Percentage of samples in which analyte was detected.
[f]LOD = Average limit of detection (instrumental noise or mean concentrations in blanks) in pg/g.

Supplemental Material, Additional modelling results for PCBs 118, 138, and 180

Table S2: Summary of predicted concentrations of 3 PCBs from the mechanistic model CoZMoMAN and their comparisons those measured in MISA and NOWAC women.

PCB cong.	Study group	Median prediction	Median discrepancy	Rank correlation r_s
118	MISA	8.31	3.76	0.31
	NOWAC	17.6	3.66	0.15
138	MISA	15.8	0.44	0.35
	NOWAC	35.7	-25.4	0.13ns
180	MISA	17.9	0.01	0.38
	NOWAC	58.3	-6.08	0.16

ns=not significant

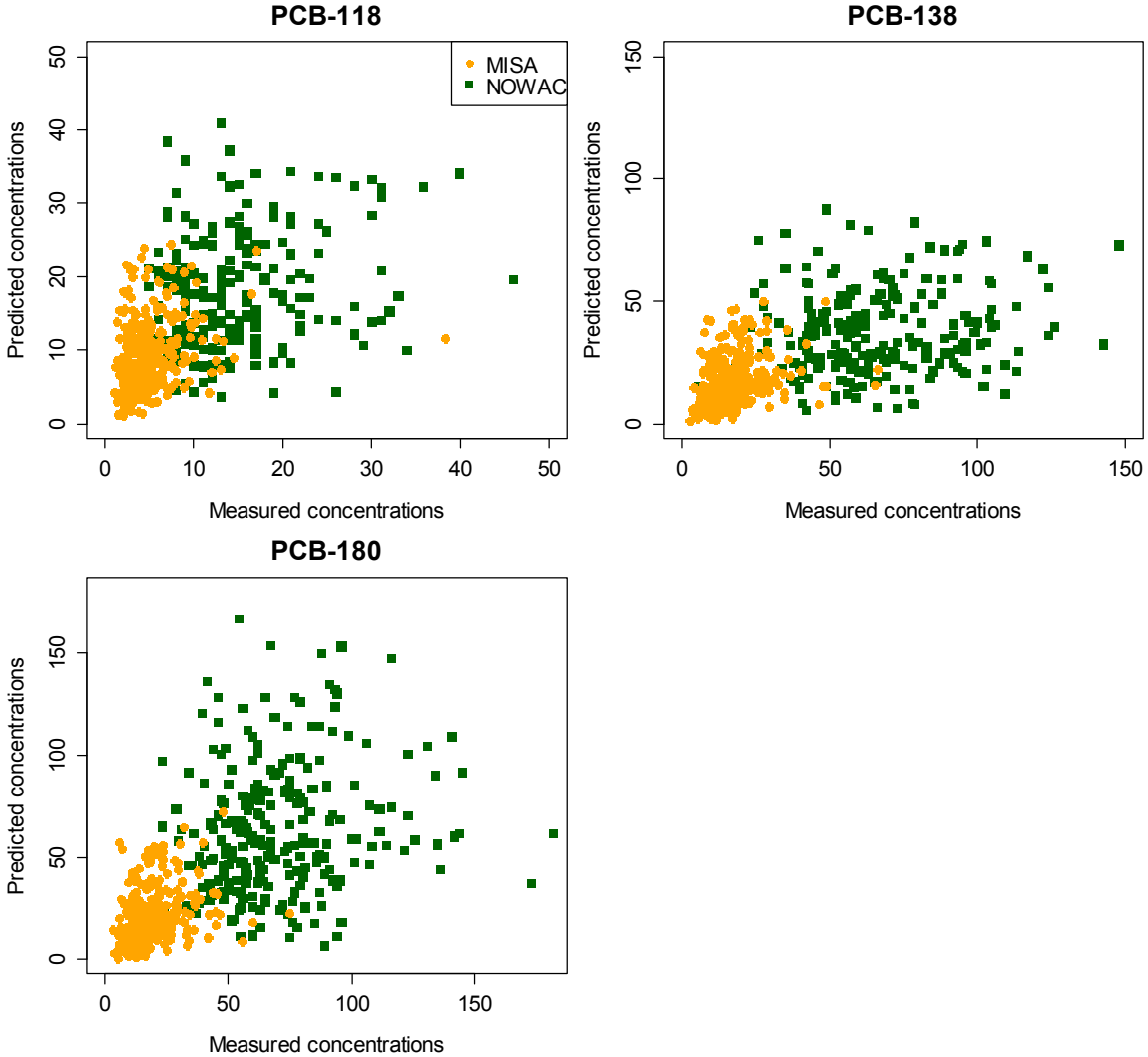

Figure S1: Measured serum concentrations (in ng/g lipid) of PCBs 118, 138 and 180 along with those predicted obtained from CoZMoMAN for the MISA (orange dots, *n*=310) and NOWAC (green squares, *n*=244) study subjects.

Supplemental Material, Predictors of discrepancies of the CoZMoMAN predictions

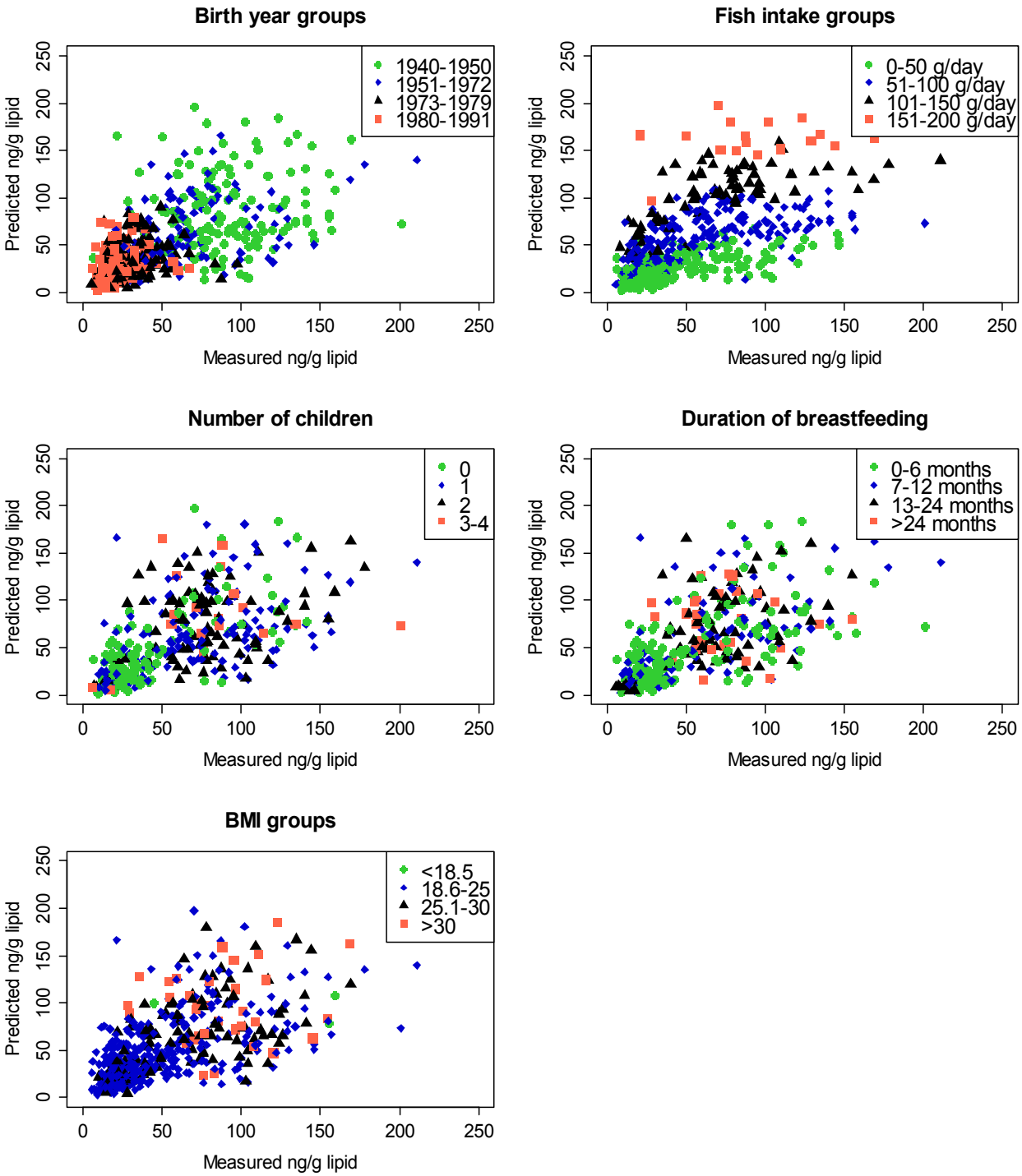

Figure S2: Comparison of between measured and predicted concentrations (in ng/g lipid) of PCB-153 according to important personal characteristics: Birth year, fish intake, number of children, duration of breastfeeding, and BMI.

Table S3: Discrepancies between measured and predicted concentrations of PCB-153 in ng/g lipid for groups of important personal characteristics plotted in Figure S2.

Variable	Group 1	Group 2	Group 3	Group 4
Birth year	*1940-1950*	*1951-1972*	*1973-1979*	*1980-1991*
	5	1	-4	-6
Fish intake	*0-50 g/day*	*51-100 g/day*	*101-150 g/day*	*151-200 g/day*
	16	-1	-30	-68
Number of children	0	1	2	3-4
	-3	4	2	-4
Duration of breastfeeding	*0-6 months*	*7-12 months*	*13-24 months*	*>24 months*
	3	0	-2	-3
BMI class	*<18.5*	*18.6-25*	*25.1-30*	*>30*
	14	-1	0	-9

Table S4: Predictors of discrepancy between measured and predicted concentrations for MISA and NOWAC women in linear regression models[a]. Models accounted for 50% and 56% of variations in model discrepancies for the MISA and NOWAC women, respectively.

Predictor	**MISA**			**NOWAC**		
	Coefficient estimate	SE[b]	p-value	Coefficient estimate	SE[b]	p-value
Birth year	0.76	0.18	***	2.92	0.53	***
Total breastfeeding	-0.88	0.18	***	0.38	0.18	*
Intake of fish[c]	0.45	0.03	***	0.83	0.05	***
Body weight	0.22	0.06	***			

[a]Intercepts for MISA and NOWAC models were significant. Further, levels of significance of predictors were as follows: '***'=p<0.001; '*'=p<0.05.
[b]SE = Standard error of estimate.
[c]Intakes represents summed fish intakes in g fresh weight/day.

Supplemental Material, Evaluation of individualised input to CoZMoMAN

Hypothetical simulations were performed where individual parameterisation of input parameters was disregarded and replaced with static values for all individuals. Dietary intake input parameters were replaced by group medians and other parameters were replaced with zero for all individuals.

Table S5: Agreements of predictions with measurements in separate simulations in which individual information was disregarded for one or several variables. In simulations including individual parameterisation of all variables the rank correlation was 0.40 and 0.13, and median discrepancy was +4.8 and -3.3 for MISA and NOWAC women, respectively,

Static input value for:	**Rank correlation r_s**		**Median discrepancy**	
	MISA	**NOWAC**	**MISA**	**NOWAC**
Birth year	0.27	0.13	+5.31	-8.47
Duration of breastfeeding	0.23	0.08ns	+11.0	-1.76
Age at childbirth	0.21	0.08ns	+12.1	-0.8
No. of children	0.21	0.08ns	+12.1	-0.8
Age at childbirth and duration of breastfeeding	0.21	0.08ns	+12.1	-0.8
Dietary intake rates	0.46	0.25	+3.81	-6.13
Duration of breastfeeding and dietary intake rates	0.37	-0.21	+11.7	-1.0
Age at childbirth and dietary intake rates	0.29	-0.31	+11.8	-0.55
No. of children and dietary intake rates	0.29	-0.31	+11.8	-0.55
Age at childbirth, duration of breastfeeding and dietary intake rates	0.29	-0.31	+11.8	-0.55

ns=not significant

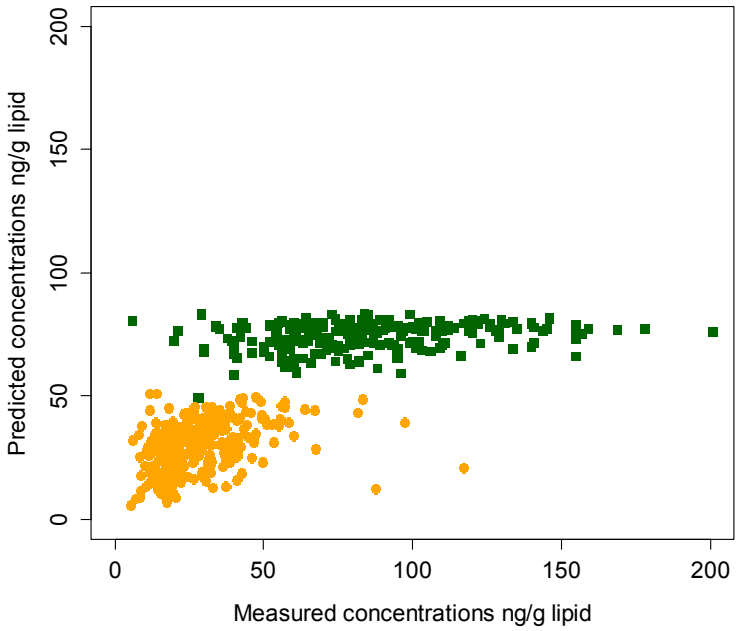

Figure S3: Measured serum concentrations of PCB-153 along with those predicted (both in ng/g lipid) obtained from CoZMoMAN when assuming median daily intakes of fish, meat and dairy products for all individuals for the MISA (orange dots, n=310) and NOWAC (green squares, n=244) study subjects.

Supplemental Material, Summary of regression analyses

- Description of regressions methods

A large number of dietary and lifestyle variables were available for MISA and NOWAC participants (305 and 165, respectively). Briefly, the demographic and lifestyle variables in both studies included birth year, number of persons in household, marital status, number of children, age at childbirths, breastfeeding, years of education, gross income, smoking status, total physical activity (scale 1–10), body weight, body height. Calculated daily intakes of many different food items as well as alcohol consumption and intakes of micronutrients were available. Several questions in questionnaires for the MISA study distinguished between the period before and during pregnancy. Although questionnaires were similar in the two studies, some questions were unique to the questionnaires used in one of the study groups, like intake of seagull eggs and previous weight loss for MISA women and indoor work place for NOWAC women. The food frequency questionnaires in the NOWAC study have been validated by several approaches (Hjartåker et al., 2007; Hjartåker et al., 1997; Parr et al., 2006) and the questionnaire in the MISA study was expanded from the NOWAC questionnaires.
Principal component analyses including dietary and lifestyle variables were initially conducted for each study group to select potential predictors of concentrations that were further assessed in linear regression models. Models were constructed separately for MISA and NOWAC women and the best models were selected based on significance of covariates and pairwise log likelihood tests.

- Summary of best fitted model coefficients

In this study, predictors differed slightly from those identified by Rylander et al. (2012) and A.S. Veyhe (personal communication), which could be due to different statistical approaches and possible confounding of dietary variables in regression models.

Rank correlations of measured PCB-153 concentrations and predictions from regression models were similar when concentrations were log-transformed in the analysis; however, the original scales were preferred. When including MISA women who consumed seagull eggs in the regressions, the same predictors were significant in addition to intakes of seagull eggs, which

then was the predictor with the largest coefficient. This is in accordance with findings of Caspersen et al. (2013). When including NOWAC women with five or more children in the regressions, model characteristics did not change considerably.

Table S6: Predictors of PCB-153 concentrations in linear regression models[a] of the MISA and NOWAC study subjects. The models for the MISA and NOWAC women accounted for 36% and 22% of variations in concentrations, respectively.

	MISA			**NOWAC**		
Predictor	Coefficient estimate	SE[b]	p-value	Coefficient estimate	SE[b]	p-value
Birth year	-1.49	0.15	***	-2.86	0.51	***
Duration of breastfeeding (mths)	-1.29	0.15	***	-0.95	0.18	***
Body weight (kg)	-0.21	0.05	***			
Intake of fish liver	11.0	3.24	***			
Intake of freshwater fish	1.23	0.27	***			
Intake of summed fish				0.09	0.05	.

[a]Intercepts for MISA and NOWAC models were significant. Further, levels of significance of predictors were as follows: '***'=p<0.001; '**'=p<0.01; '*'=p<0.05; '.'=p<0.1.
[b]SE = Standard error of estimate

Supplemental Material, References

Breivik, K, Czub, G, McLachlan, MS, Wania, F. 2010. Towards an understanding of the link between environmental emissions and human body burdens of PCBs using CoZMoMAN. Environ Int 36(1):85-91.

Caspersen, IH, Knutsen, HK, Brantsæter, AL, Haugen, M, Alexander, J, Meltzer, HM, et al. 2013. Dietary exposure to dioxins and PCBs in a large cohort of pregnant women: Results from the Norwegian mother and child cohort study (MoBa). Environ Int 59:398-407.

Czub, G, McLachlan, MS. 2004. A food chain model to predict the levels of lipophilic organic contaminants in humans. Environ Toxicol Chem 23(10):2356-2366.

Hjartåker, A, Andersen, LF, Lund, E. 2007. Comparison of diet measures from a food-frequency questionnaire with measures from repeated 24-hour dietary recalls. The Norwegian women and cancer study. Public Health Nutr 10(10):1094-1103.

Hjartåker, A, Lund, E, Bjerve, K. 1997. Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. Eur J Clin Nutr 51(11):736-742.

Nøst, TH, Breivik, K, Fuskevåg, O-M, Nieboer, E, Odland, JØ, Sandanger, TM. 2013. Persistent organic pollutants in Norwegian men from 1979 to 2007: Intraindividual changes, age–period–cohort effects, and model predictions. Environ Health Perspect 121(11-12):1292–1298.

Norwegian Food Safety Authority. The Norwegian Food Composition Table. Available: http://www.matvaretabellen.no/?language=en [accessed 30 January 2014].

Norwegian National Institute of Nutrition and Seafood Research. Documentation and Surveillance program, Seafood data – Undesirables. Available: http://www.nifes.no/index.php?page_id=137&lang_id=2 [accessed 20 March 2014].

Parr, CL, Veierød, MB, Laake, P, Lund, E, Hjartåker, A. 2006. Test-retest reproducibility of a food frequency questionnaire (FFQ) and estimated effects on disease risk in the Norwegian women and cancer study (NOWAC). Nutr J 5(1):4.

Rylander, C, Lund, E, Frøyland, L, Sandanger, TM. 2012. Predictors of PCP, OH-PCBs, PCBs and chlorinated pesticides in a general female Norwegian population. Environ Int 43:13-20.

Veyhe, AS, Hansen, S, Sandanger, TM, Nieboer, E, Odland, JØ. 2012. The Northern Norway mother-and-child contaminant cohort study: Implementation, population characteristics and summary of dietary findings. Int J Circumpolar Health 71.