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Predicting human plasma concentrations of persistent organic pollutants from dietary intake and socio-demographic information in the Norwegian Women and Cancer study

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ABSTRACT

Background: Concentrations of persistent organic pollutants (POPs) in humans are influenced by a large number of factors including birth year, reproductive history and diet. Accordingly, information on dietary habits and socio-demographic variables may predict plasma concentrations of POPs, thus enabling studies on health effects in large epidemiological studies, without performing time consuming and expensive chemical analyses on entire cohorts.

Aims: To develop and evaluate statistical models for predicting concentrations of POPs in participants of the Norwegian Women and Cancer (NOWAC) study, using questionnaire information and measured plasma POP concentrations.

Materials and methods: Information on estimated dietary intakes and socio-demographic variables from four different questionnaires (in 1991, 1994, 2004 and 2005) were obtained from participants in the NOWAC study. We measured POP concentrations in a total of 367 blood samples from 2005 and built multivariable linear regression models for *p,p′*-DDE, PCB-118, -138, -153, -180 and summed PCB concentrations in one subsample (N = 259) and evaluated the models in another subsample (N = 108). Measured and predicted values were compared using correlation coefficients and inter-method agreement was evaluated using weighted Cohen's κ for tertile categorization.

Results: Median POP concentrations in the population ranged from 13 ng/g lipid to 162 ng/g lipid (lowest for PCB-118 and highest for *p,p′*-DDE). Common predictors for all POPs were birth year, breastfeeding and the weight-related variables (BMI or weight change), whereas influential dietary variables differed and were of varying importance. The predicted plasma concentrations were significantly correlated with the measured values (r_s = 0.24, 0.33, 0.41, 0.50, 0.56, and 0.54 for *p,p′*-DDE, PCB-118, -138, 153, -180 and summed PCBs, respectively). Tertiles of predicted plasma concentrations displayed significant, but varying agreement with measured concentrations (Weighted Cohen's κ = 0.19, 0.22, 0.33, 0.42, 0.45, and 0.50 respectively).

Conclusion: Predicted plasma concentrations of certain PCBs showed good precision (Kw > 0.4) when compared to measured concentrations. Thus, the models can be used to classify NOWAC participants into high, medium and low PCB exposure groups.

1. Background

Polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) such as *p,p′*-DDE, are classified as persistent organic pollutants (POPs), and are chemicals that were largely manufactured and emitted to the environment during the 20th century (Lohmann et al., 2007). When released into the environment, POPs accumulate in food chains; hence, an important exposure source of POPs for the general population is diet, especially the consumption of fatty foods of animal origin (Bergkvist et al., 2008; Linares et al., 2010). The production and use of several OCPs and PCBs have declined markedly since the late 1970s due to international restrictions and bans, but many of these chemicals resist biodegradation, and continue to accumulate and magnify in food chains for years (Linares et al., 2010). As a result, the impact of diet and

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lifestyle will be important for the human body burden of POPs now and in the future.

High exposures to POPs have been demonstrated to cause harmful effects in humans, whereas health effects of background exposures in the general population have been inconsistent (Lee et al., 2014; Lee et al., 2017; Longnecker et al., 1997; Yang et al., 2017). The inconsistent findings in background exposed populations may be due to the study design, which is often cross-sectional, and the inclusion of a small number of participants as POP analyses are expensive and time-consuming. Thus, predicting concentrations as opposed to measuring them could enable studies on health effects of POPs in large epidemiological studies. As the general population of Norway are mostly exposed to low levels of POPs through their diet, dietary- and lifestyle-patterns may be strong predictors of plasma concentrations of POPs. The aims of this study were therefore to; i) develop regression models for predicting concentrations of the most common POPs in human plasma in a subsample of a Norwegian female study cohort; and ii) evaluate the accuracy of the models by comparing predicted and measured plasma concentrations in another subsample of the same cohort.

2. Materials and methods

2.1. Study population

The women included in the present study were all participants of the Norwegian Women and Cancer Study (NOWAC) (Lund et al., 2008). The participants were randomly selected from the central person registry in Norway, and invited to participate in the study with an invitational letter sent to their home address. Currently, the NOWAC cohort consists of > 170,000 Norwegian women aged 30–70 years that are representative for the general female population in Norway (Lund et al., 2008). All participants in NOWAC have answered at least one detailed questionnaire about diet and lifestyle and approximately 50,000 have also donated a blood sample. The latter constitute the NOWAC postgenome cohort (Lund et al., 2008). At the time of blood sampling, the participants additionally filled out a two-page questionnaire regarding current health status and use of medication. From the 50,000 women who delivered a blood sample, a random sample of 500 women (born between 1943 and 1957, blood drawn in 2005) were selected for analysis of fatty acids, gene expressions, sex hormones and environmental contaminants. Detailed information about the study sample and the blood collection procedures have been reported elsewhere (Waaseth et al., 2008). Due to budget limitations, Rylander et al. (2012) analyzed and published POP results for 311 of these samples and 259 of these were further used in this study for development of the regression models according to dataset completeness (referred to as the model sample). POP concentrations from another subsample of 108 NOWAC women (born between 1943 and 1957, blood drawn between 2003 and 2006) were selected from the 50,000 NOWAC postgenome cohort as controls in a case-control study conducted by Rylander et al. (2015). This subsample was used to assess the validity of the models (referred to as the validation sample). The external validity of NOWAC has been validated by linkage to national registers. The results showed minor differences between responders and the total sample of women, no differences in life-style factors and there were no major source of selection bias (Lund et al., 2003).

2.2. Questionnaire data

Each participant answered up to four questionnaires in 1991, 1998, 2004 and 2005. Included questions and level of details have varied between questionnaires. In 2004, the participants answered the NOWAC food frequency questionnaire (FFQ) where they were asked to record how often they consumed > 90 different foodstuffs during the preceding year. The FFQ has special emphasis on fish consumption. The NOWAC FFQ has been validated by four repeated 24 h recalls in 283 women (Hjartaker et al., 2007) where the FFQ performed well in estimating daily intake of a number of food items. Reported fish intake has also been validated against serum phospholipid n-3 fatty acid composition as biomarkers for fish consumption (Hjartaker et al., 1997). Additionally, the reproducibility of the FFQ has been tested in a test-retest study, assessing reproducibility for single questions, food groups, total energy intake, and nutrients. The mean daily intake of energy, protein, carbohydrates, and most foods was slightly lower in the retest. However, the overall reproducibility (estimated reliability coefficients ranged from 0.5–0.8) of intakes for food groups was considered good (Parr et al., 2006). Body weight and height were reported in 1991, 1998, 2004 and 2005, and total weight change from 1991 to 2005 (three delta weight change calculations) was calculated as the mean weight change in kilos per year. Self-reported information on height and weight in the NOWAC cohort have been validated against measurements conducted by trained health personnel and there was substantial agreement between self-reported values and those measured by medical staff (Skeie et al., 2015). The reported dietary and lifestyle variables from the questionnaires were evaluated as possible predictors of POP concentrations, and the variables used in the analyses presented in Tables 1 and 2 were used as continuous variables, except for current smoking, that was dichotomous (yes or no).

2.3. Chemical analyses

All samples were extracted and cleaned-up using a modified method

Table 1
Demographic characteristics of NOWAC women.

	Model sample (N = 259)				Validation sample (N = 108)			
	Mean	SD	Median	Percentiles (5, 95)	Mean	SD	Median	Percentiles (5, 95)
Birth year	1949	4	1949	1944, 1956	1948	4	1947	1943, 1957
Age	56	4	56	49, 61	57	4	58	48, 62
Years of education	12	3.2	12	8, 18	12	3	12	7, 17
Number of children	2	1	2	1, 4	3	1	2	1, 5
Breastfeeding (months)	13	12	10	0, 31	14	11	12	0, 37
Years since last birth at blood draw	26	6.3	26	16, 37	27	7	28	15, 37
BMI 1991	23.2	3.5	22.7	18.9, 30.6	23.7	3.5	23.0	19.3, 29.7
BMI 1998	24.8	4.0	24.1	19.4, 32.1	24.8	3.7	23.9	20.2, 32.0
BMI 2004	25.7	4.4	24.6	29.9, 33.1	25.8	3.9	25.2	20.4, 33.2
BMI 2005 (at blood draw)	25.8	4.4	24.9	20.0, 33.5	25.7	4.2	24.9	20.8, 33.9
Weight change 1991–2005 (kilograms)	7.2	6.7	6.0	−2.4, 20	5.7	6.6	4.0	−4.0, 17.8
Weight change (kg per year)	0.5	0.5	0.4	−0.2, 1.4	0.4	0.5	0.3	−0.3, 1.3
Total lipids (g/L)	5.8	1.1	5.6	4.1, 7.9	6.3	1.2	6.2	4.5, 8.3
	Yes/no	%			Yes/No	%		
Smoking	71/187	28/72			21/87	19/81		

Table 2
Dietary information of the NOWAC women represented by dietary intakes of a range of major food groups and food items.

	Model sample (N = 259)			Validation sample (N = 108)		
Intake (grams per day)	N%[a]	Median	Percentiles (5, 95)	N%[a]	Median	Percentiles (5, 95)
Alcohol	85	33.7	0, 220	81	22.9	0, 297
Spirits	29	0	0, 5,72	32	0	0, 5,73
Bread and cereals	100	131	39, 240	99	140	36, 211
Butter and margarine	70	9.64	0, 32	61	8.57	0, 30
Cheese	97	20.0	8, 80	93	20.0	0, 68
Chocolate	84	3.29	0, 25	78	3.08	0, 20
Coffee	91	525	0, 1365	93	525	0, 1422
Desserts	72	5.94	0, 37	73	7.95	0, 37
Eggs	87	16.8	0, 46	89	16.8	0, 53
Fish oil[b]	21	0	0, 11	26	0	0, 11
Fish[c]	98	41.0	6, 119	98	43.9	13, 156
Fat fish[d]	90	12.9	0, 49.5	93	16.1	0., 57.8
Fish liver	28	0	0, 0.74	41	0	0, 1.16
Fish spread	82	8.60	0, 32	84	9.19	0, 31
Lean fish[e]	93	20.5	0, 67.9	94	23.7	0, 81.5
Processed fish[f]	96	19.9	2, 62	94	21.5	0, 76
Roe	5	0.60	0, 1.68	67	0.60	0, 2.97
Shellfish	64	3.54	0, 15	58	3.54	0, 9
Fruits	99	195	23, 492	99	177	0, 550
Jam	69	5.70	0, 20	69	5.72	0, 50
Mayo	29	0	0, 21	46	0	0, 8.6
Meat[g]	100	109	32, 195	98	109	36, 188
Reindeer meat	15	0	0, 8.72	15	0	0, 7.41
Milk products	100	147	19, 628	99	213	25, 641
Other porridges	35	0	0, 140	44	0	0, 35
Pasta	76	12.1	0, 52	69	12.1	0, 40
Pastry	93	29.1	0, 84	96	35.6	5, 104
Porridge from rice	53	11.6	0, 50	67	11.6	0, 50
Potato	9	63.0	0, 189	93	126	0, 189
Rice	86	10.0	0, 43	78	10.1	0, 43
Salty snacks	73	5.02	0, 16	64	3.01	0, 16
Sauce to fish	91	5.94	0, 25	93	6.22	0, 28
Sauce to meat	93	9.13	0, 43	94	8.30	0, 37
Soft drinks	82	150	0, 735	81	120	0, 525
Soup	71	33.5	0, 88	89	33.5	0, 136
Vegetables	100	168	50, 413	99	139	42, 366
Water	98	525	105, 1680	97	525	105, 1365
Calories per day (kcal/day)	100	1680	1039, 2392	100	1718	1041, 2343

[a] The percentage of consumers.
[b] Cod liver oil as food supplement.
[c] Includes fatty fish, fish spread, lean fish, other fish, fish liver, processed fish, roe and shellfish.
[d] Includes catfish, salmon, mackerel and herring.
[e] Includes boiled and fried cod.
[f] Includes fishcake, fish gratin, fried fish and other fish dishes.
[g] Includes pork chops, roast, filet of meat (beef and reindeer), chicken, processed meat and meat spread.

from Sandanger et al. (2007). Details on the procedures are described elsewhere (Rylander et al., 2012; Rylander et al., 2015). In brief, 0.5–1 mL of plasma sample was mixed with 100 μL of 13C-labelled PCB and pesticide mixture (10 pg/μL) in methanol (Merck, Darmstadt, Germany). The following 13C-labelled PCBs and chlorinated pesticides were used as internal standards; PCB 101, 118, 153 and 180, and 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene (*p,p′*-DDE). Further, POPs were extracted using hexane (2 × 6 mL), ethanol (2 mL) and saturated ammonium sulphate solution (2 mL). The POP extracts were cleaned up using 1 g of activated florisil columns and an automated liquid-handling system (Zymark 3-Module RapidTrace SPE Workstation) before PCBs in the extracts were identified and quantified 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 the PCB results. Lipids were determined enzymatically, and the summed concentrations of lipids was calculated as follows: Total lipids (mg/dL) = 1.677(total − free cholesterol) + free cholesterol + triglycerides + phospholipids (Akins et al., 1989). All presented POP concentrations were lipid adjusted.

Extraction and analyses of *p,p′*-DDE and PCBs in the model sample were performed at NILU - The Norwegian Institute for Air Research in Tromsø, whereas the extraction and analyses in the validation sample were performed at Centre de Toxicologie de Quebec, Institut National de santé publique de Québec in Canada. The methods were comparable, and both laboratories participate in the Arctic Monitoring and Assessment Programme ringtest for POPs in human serum, an international comparison program organized by Institut National de Santé Publique du Québec, Canada (Institut national de santé publique du Québec, 2014). Interlaboratory comparisons indicated that the uncertainties of analyses were within ± 15–20% of the assigned values for the reference samples. However, NILU reported PCB-138 concentrations that included those for PCB-163 due to co-elution, and thus report higher concentrations of this congener compared to Centre de Toxicologie de Quebec.

2.4. Statistical analyses

Partial least square (PLS) regressions were used to identify the variables that were associated with plasma concentrations of POPs in the model sample. The data structure resulted in variables with generally low variable of importance (VIP) values, thus a threshold of > 0.4 was selected for variables to be included in the linear regression models. (PLS) regressions were used to identify variables that were associated with plasma concentrations of POPs in the model sample. The data structure resulted in variables with generally low variable of importance (VIP) values. A threshold of VIP value > 0.4 were selected for variables to be included in the linear regression models. We built separate models for *p,p′*-DDE, PCB-118, -138, -153, -180 and summed PCBs. We refined the linear regression models by including those variables that contributed significantly ($p < 0.05$, method: enter) to the overall explained adjusted variance (R-square). Parity and total duration of breastfeeding were highly correlated, and to avoid multicollinearity, breastfeeding was selected in the final models to represent reproductive history. Similarly, the variable “time passed since last child birth” was highly correlated to birth year, and thus birth year, the strongest predictor of the two, was selected. The different BMI calculated from self-reported weight and height in 1991, 1998, 2004 and 2005 were highly correlated. BMI reported in 2005 was the strongest predictor of *p,p′*-DDE concentrations and therefore included in the model. Total weight change per year (calculated by summing the weight change per individual from 1991 to 2005) was included in the PCB models. Regression analyses were run with and without transformed variables as POP concentrations and dietary variables were mostly non-normally distributed. Potential interaction was also investigated. The number of subjects included from the model sample varied between models (N = 234–250) according to completeness of the dataset.

Predicted concentrations were derived for each individual in the validation sample using the best-fitted linear regression models in the model sample. We evaluated the models by comparing predicted and measured concentrations using scatter plots and Spearman's rank correlation coefficients (r_s). In addition, measured and predicted concentrations were divided into tertiles with equal number of participants (classified with low, medium and high exposure), and the weighted Cohen's κ (K_w) was subsequently calculated as a measure of inter-method agreement for the tertile categorization. K_w represents the degree of consistency between the measured and predicted concentrations, and indicates the number of samples that are classified into the same tertiles. K_w in the range of 0.61–0.80 is considered good, K_w between 0.41 and 0.60 is moderately good and < 0.40 is considered poor

(Altman, 1991). Statistical analyses were performed using SPSS statistic software, ver. 24 (IBM SPSS Inc. Chicago, IL, USA) and a statistical significance threshold of $p < 0.05$ was used.

3. Results

3.1. Population characteristics

Socio-demographic characteristics and dietary information in the two subsamples of the NOWAC women are summarized in Tables 1, and 2, respectively. The participants answered > 90 questions about different foods, and a selection of major food categories are presented in Table 2. Characteristics and daily intakes of various food groups were similar for the two samples; however, the model sample contained a higher proportion of smokers.

3.2. POP concentrations

All participants delivered blood samples in 2005 and the measured POP concentrations in the two sub-samples are provided in Table S1 in the Supplemental material. For both sub-samples, the highest concentrations were detected for *p,p′*-DDE followed by PCB-153 > PCB-180 > PCB-138 and PCB-118. Median concentrations of *p,p′*-DDE, PCB-138 and PCB-180 were slightly higher in the model sample compared to the validation sample (163 versus 130, 61 versus 41, and 62 versus 55, ng/g lipid, respectively). Median concentrations of PCB-153 and PCB-118 were similar (81.9 versus 79.2, and 12.9 versus 13.0 ng/g lipid, respectively). The correlation between the different POPs were high (ranging from 0.6–0.9) and similar within the two sub-samples.

3.3. Regression models

Two PLS models (one for summed PCBs and one for *p,p′*-DDE) included all reported socio-demographic and dietary variables (Figs. S1 and S2 in the Supplemental material). The first two principal components (PCs) explained 50% and 37% of the variation in summed PCBs and *p,p′*-DDE concentrations, respectively. Variables of high importance as indicated in the PLS plots where further confirmed in linear regression models. Socio-demographic variables described slightly more (R^2 range 13–32%) of the variation in concentrations of the different compounds compared to the dietary variables (R^2 range 9–20%), except for PCB-118 (20 of 32% total explained variance). The significant socio-demographic predictors were birth year, breastfeeding, weight change and BMI at blood draw, whereas the dietary variables differed according to compound (Table 3). Common dietary predictors for PCBs were the marine food variables. For instance, for PCB-118, -153 and summed PCB models, the respective plasma concentrations increased by 6.95, 26.4 and 55.9 ng/g lipid per 1 g intake of fish liver (50% fat) per day. For lean fish (muscle, < 1% fat), the plasma concentrations of PCB-118, -138, -153 and summed PCBs increased by 0.10, 0.38, 0.29 and 0.84 ng/g lipid for every increase in intake in g/day, respectively. Fatty fish (muscle, 5% fat) was not identified as a predictor for POP concentrations but intake of fish oil (100% fat) as food supplement was a predictor for PCB-118 and -180. Residuals in the regression models were normally distributed when untransformed variables were used, and result were similar regardless of using untransformed- or transformed variables. Further, there was a weak but significant interaction between weight change and BMI > 35, but including an interaction term in the models did not improve the models, neither did the model parameters change when stratifying on BMI.

There were strong positive correlations between calculated BMIs at the four different time points (r_s = 0.84–0.97), whereas the correlation between weight change and BMI increased during the period, r_s = 0.35, 0.51 and 0.59 in 1998, 2004 and 2005, respectively. Weight change in the period 1991–2005 were inversely associated with plasma concentrations of the PCBs, where each kilogram increase in weight per year resulted in increased sum-PCB concentration of 68.7 ng/g lipid. Likewise, a weight loss of 1 k per year in the period resulted in a decreased sum PCB concentrations of 68.7 ng/g lipid. Further, PCBs and BMI were positively correlated only when adjusting for the weight change. The opposite was observed for *p,p′*-DDE, where concentrations were positively correlated to BMI at blood draw, and inversely correlated to weight change when adjusting for BMI.

Table 3
Linear regression models for *p,p′*-DDE, PCBs and summed PCBs in the model sample.

	Models					
	PCB-118	PCB-138	PCB-153	PCB-180	Summed PCBs	*p,p′*-DDE
Constant	45.9	183	255	214	678	570
Predictors[a]	Regression coefficients (β-values)[b]					
Birth year	−0.61	−2.09	−3.03	−2.55	−8.20	−9.10
Breastfeeding (months)		−0.36	−0.62	−0.39	−2.05	−2.03
Weight change kg/year	−2.73	−17.6	−25,3	−21,3	−68.7	
BMI at blood draw						6.24
Adjusted R^2 (%)[c]	13	20	25	32	27	13
Boiled cod	0.10	0.38	0.29		0.84	
Brown cheese		−0.47	−0.60	−0.41	−1.29	
Butter on bread				0.82		
Coffee	−0.004					
Fish[d]				0.09		
Fishcakes			0.48			
Fish liver	6.95		26.4		55.9	
Fish oil	0.54			1.21		
Jam		−0.29	−0.47	−0.25	−1.25	
Cabbage		0.91	1.10	0.88	2.70	
Milk and yoghurt			0.02			
Pancakes		−0.53	−0.49		−1.29	
Pudding		0.82				
Reindeer meat	−0.08		−0.25			4.30
Sausage	0.09					
Spirits			1.37		2.89	5.43
Steak					−2.15	
Vegetables mix			−0.36		−0.81	
Wheat products						−0.36
White cheese	−0.09					
Yoghurt	0.04					
Adjusted R^2 (%)[e]	33	34	44	43	44	22
N	250	234	234	234	234	237

[a] Predictors were included as continuous variables.
[b] β-values express the change in POP concentrations (ng/g lipid) per unit increase (1 g/day for the dietary variables) in the predictor.
[c] Proportion of the variance in concentrations explained by socio-demographic predictors.
[d] Includes fat fish, fish spread, lean fish (boiled cod), other fish, fish liver, processed fish, roe and shellfish.
[e] Proportion of the variance in concentrations explained by socio-demographic and foodstuff predictors.

3.4. Evaluation of the regression models

The predicted plasma concentrations were significantly correlated with the measured values (Table 4). PCB-180 displayed the highest correlation coefficient followed by summed PCBs > PCB-153 > PCB-138 > PCB-118 and *p,p′*-DDE. The predicted median concentrations were higher than the measured concentrations for all compounds. All the models generally underestimated the lowest concentrations and

Table 4
Measured and predicted POP concentrations (ng/g lipid) in the validation sample (N = 108).

	Measured concentrations	Predicted concentrations	Correlation r_s	Correct tertile %	Weighted Cohen's K
	Median (5, 95 percentiles)	Median (5, 95 percentiles)			
Summed PCBs	190 (105, 379)	220 (74.2, 351)	0.54	61	0.50
PCB-180	56.1 (30.5, 106)	83.6 (50.4, 113)	0.56	57	0.45
PCB-153	80.0 (43.5, 165)	96.6 (44.1, 149)	0.50	59	0.42
PCB-138	40.9 (18.1, 88.2)	76.1 (34.1, 112)	0.41	49	0.33
PCB-118	13.2 (6.11, 30.8)	16.2 (5.64, 28.9)	0.33	39	0.22
p,p′-DDE	130 (36.7, 589)	213 (91.1, 383)	0.24	42	0.19

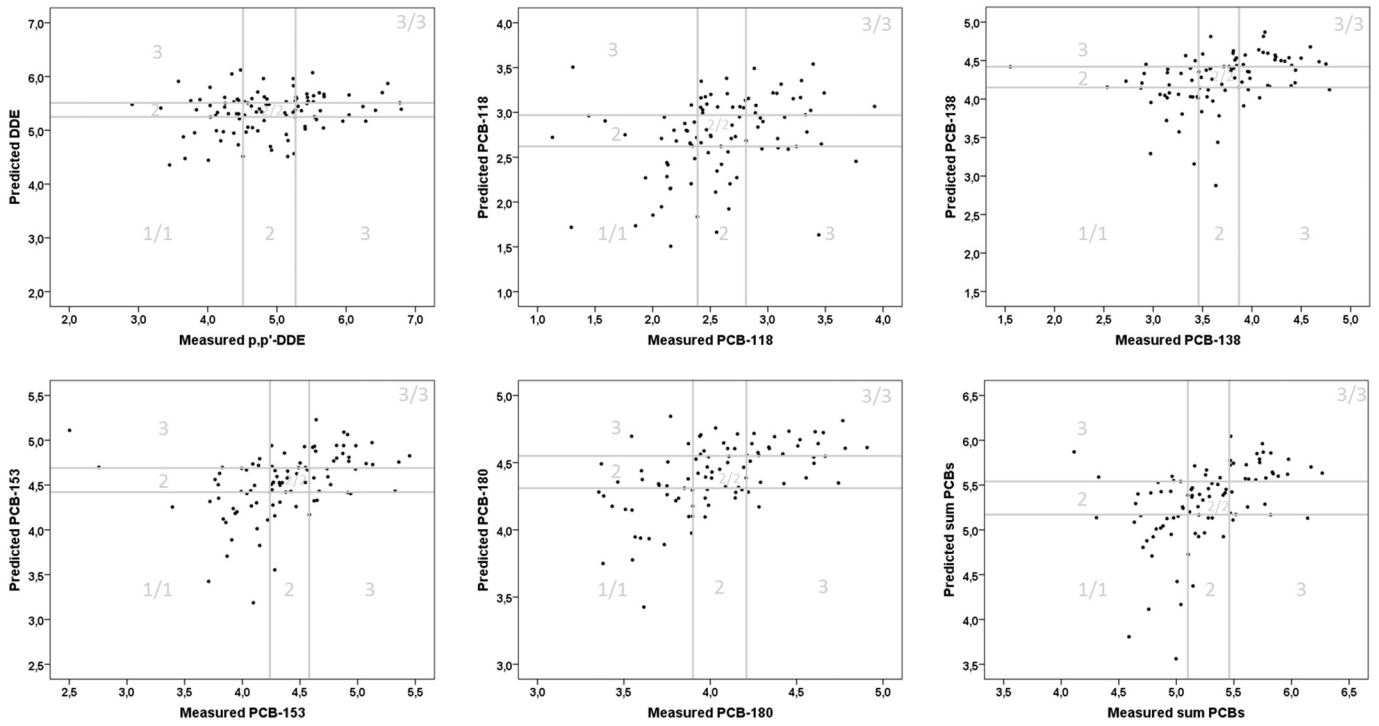

Fig. 1. Scatter plot of measured versus predicted *p,p′*-DDE, PCB-118, -138, -153, -180 and summed PCB concentrations. Ln transformed measured concentrations are presented on the x-axis and ln transformed predicted concentrations on the y-axis. The light grey lines represent the borderlines for the tertiles.

overestimate the highest concentrations. The inter-method agreement, evaluated by K_w for tertile categorization (Table 4) was considered acceptable (≥0.4, moderately good) (Altman, 1991) for PCB-153, PCB-180 and summed PCBs. Fifty nine, 57 and 61% of the individuals were categorized into the correct tertile (Table 4 and Fig. 1), respectively, and > 87% of those misclassified were classified into the adjacent tertile.

4. Discussion

4.1. Main findings

In this study, we have developed regression models for predicting plasma concentrations of POPs based on questionnaire data on socio-demographic factors and dietary intake in the NOWAC cohort. Based on correlations ($r_s \geq 0.5$) and moderately good inter-method agreements for the tertile categorization ($K_w \geq 0.4$), we conclude that the PCB models can predict plasma concentrations of PCB-153, PCB-180 and summed PCBs, and rank subjects according to high, medium or low exposure of these compounds. The present results indicate that these models represent a unique opportunity to evaluate the risk of lifestyle diseases in relation to POP exposure in the NOWAC cohort.

In this study, we found that the most important predictors for POP concentrations were birth year, breastfeeding (except for PCB-118), BMI and weight change. Dietary intake had slightly less influence on the body burdens of POPs (except for PCB-118), and differed between compounds. The identified predictors are in line with findings in other studies, especially in cohorts including only women, where birth year, parity, breastfeeding, BMI and marine food intake have been commonly reported (Caspersen et al., 2016; Lauritzen et al., 2016; Polder et al., 2009; Veyhe et al., 2015). Predictors of PCB-118 concentrations were different from the other PCBs and this was also observed in two similar studies from Scandinavia also building regression models based on questionnaire data (Bergkvist et al., 2012; Kvalem et al., 2012). This observation may be explained by the dioxin-like properties of PCB-118, accumulation patterns in biota and the shorter half-life compared to the other PCBs (Milbrath et al., 2009).

The regression models for PCBs explained 33–44% of the variation in concentrations and these results are in line with the results reported by Bergkvist et al. (2008) and Kvalem et al. (2009). The proportion of explained variance increased in our regression models with increasing PCB chlorination, which is also in accordance with the studies by Bergkvist et al. and Kvalem et al. Further, our PCB-153 model explained more of the variance in concentrations compared to mechanistic model simulations of PCB-153 based on time-variant PCB emission estimates, performed by Nøst and colleagues on the same NOWAC women as our model sample (Nost et al., 2016).

Plasma concentrations of *p,p′*-DDE were not satisfactory described

by our model where only 22% of the variance in concentrations was explained by the sociodemographic and dietary variables. The most important predictors for *p,p′*-DDE were birth year and BMI at blood draw. Foods of marine origin had no impact, and these results agree with other studies investigating predictors of *p,p′*-DDE in Scandinavian and American women (Moysich et al., 2002; Rylander et al., 2012; Vaclavik et al., 2006; Vo et al., 2008). The difference in production history, time of peak exposure, as well as intrinsic half-lives between PCBs and *p,p′*-DDT/*p,p′*-DDE, may explain why dietary exposure may be of less importance for *p,p′*-DDE concentrations compared to PCBs (Breivik et al., 2007; Schenker et al., 2008).

4.2. Predicted versus measured concentrations

The predicted plasma concentrations of POPs were significantly correlated with the measured values with r_s ranging from 0.24–0.56. Inter-method agreement evaluated with K_w was considered moderately good (≥ 0.4) for PCB-153, PCB-180 and summed PCBs, and poor for *p,p′*-DDE, PCB-118 and PCB-138. When comparing measured and predicted concentrations, for example for the sum PCB model (Table 4), 39% of the individuals were classified into the wrong tertile. In epidemiological studies assessing the effect of estimated POP concentrations on a certain disease endpoint using a cohort design, such non-differential misclassification of exposure may cause lead to an attenuation of the risk estimates (relative risks) towards the null (Bhopal, 2008). However, in the present study, approximately 87% of those misclassified were classified into the adjacent tertile. This is also evident as the prediction models generally underestimated the lowest concentrations and overestimate the highest concentrations. Accordingly, the model will be able to divide participant into high or low exposure fairly well.

The agreement between predicted and measured concentrations was similar or better compared to previous attempts to predict POP concentrations based on dietary and socio-demographic information. The correlations between predicted and measured PCB concentrations in our study were in the same range as those reported by Bergkvist et al. (2012) (r_s range of 0.18–0.58 between FFQ-based exposure estimates and measured concentrations), but lower than those reported by Kvalem et al. (2012) (r_s range of 0.65–0.75). The study by Bergkvist et al. included women with similar age as the present study, whilst men and women with similar age were included in the study by Kvalem et al. As opposed to our study where the dietary variables were included directly into the regression models, the regression models in the two studies were based on estimated POP intake calculated from reported dietary intakes and measured POP concentrations in various foods. The different approaches may explain the slightly different results in our studies. Further, Kvalem et al. built and validated their prediction model on subjects classified as high-consumers of fish. Subsequently diet, and especially fish, were the most important predictors of POPs in their models and may explain the higher predictive power in their models (Kw in the range 0.58–0.65). Our regression models overestimated median POP concentrations compared to median measured concentrations for all compounds, which was also reported by Kvalem and Bergkvist. This can be due to variance from different sources; e.g. differences in sample size for the model- and validation-samples, under and/or over reporting of food intake, and/or analytical variance within and between laboratories. Compared to mechanistic models, the regression based estimations here predicted PCB-153 concentrations more accurately compared to the CoZMoMAN model when comparing correlations ($r_s = 0.50$ versus 0.13, respectively), and inter-method agreement (Kw = 0.42 versus 0.12, respectively). This is likely because our regression model included predictors that were not possible to use as individual input parameterization in mechanistic models such as CoZMoMAN (e.g. weight change, BMI, breastfeeding length and detailed dietary intake data) (Breivik et al., 2010). Further, predicted and measured PCB concentrations in our models were in the same range as reported correlations between mechanistically predicted and measured PCBs ($r_s = 0.17–0.47$) in women from Canada (Binnington et al., 2016). Thus, attempts to predict concentrations based on diet and life-style information derived from either statistical regressions or e.g. mechanistic modelling are currently comparable in terms of agreement with empirical measurements.

The correlations between the different PCB congeners measured in this study were high, which was also reported in similar studies from Norway (Berg et al., 2017; Nøst et al., 2013). This result justifies the use of summed PCBs or PCB-153 predictions as representatives of highly chlorinated PCB congener exposure in larger cohorts. In fact, within the NOWAC cohort, we have the opportunity to apply the prediction model to about 24,000 women who answered a questionnaire in 2004/2005 and were followed-up in relation to lifestyle and diseases as late as in 2017. Thus, when the results from the follow-up are finalized we will be able to estimate POP exposure (in 2004/2005) prior to disease outcome in a large sample of women. Still, using summed PCB concentrations in studies of disease outcomes assumes similar effect mechanisms for the different PCBs.

4.3. Sociodemographic predictors of POP concentrations

Birth year, breastfeeding, BMI and weight change were the strongest predictors for plasma concentrations of the measured POPs. POP concentrations were higher in older women, thus concentrations were inversely associated to birth year, which likely reflects birth year dependent past exposures (Alcock et al., 2000; Nøst et al., 2013; Quinn and Wania, 2012) as the NOWAC women were born during a period of large-scale production and use of many pesticides and PCBs (Breivik et al., 2016; Nøst et al., 2013; Schenker et al., 2008). Further, breastfeeding was an important predictor for all compounds except for PCB-118, whereas parity was not strongly associated with any compounds. This might reflect a higher loss of POPs from breastfeeding relative to trans-placental transfer, as breast-feeding can reduce a woman's body burden considerably (Schecter et al., 1998). Another explanation can be the small variance in parity amongst the women in this study.

BMI and weight change were important predictors for all compounds and weight change was the most important predictor in the PCB models, indicating lower PCB concentration with increasing body weight. This is in accordance with studies that have demonstrated that weight gain leads to decreased PCB concentrations in plasma due to increased amounts of adipose tissues (Schildkraut et al., 1999; Wolff et al., 2005). Still, reports of associations between POP concentrations and BMI or body weight vary in the literature. In contrast with the observations for PCBs, BMI at blood draw was the most important predictor for *p,p′*-DDE. This observation, could however be explained by slower elimination rates of *p,p′*-DDE in people with higher body weight as suggested by Wolff et al. (2007) and Wood et al. (2016). Thus, the complex relationship between POP concentrations, weight change and BMI warrants further examination in longitudinal studies. Overall, our results underline the importance of considering previous weight change as a potential predictor of POP exposure, and that the interpretation of the relationships between weight change, BMI and POPs is highly complex when relying on a single blood sample as in most studies assessing human POP concentrations.

4.4. Dietary predictors

Several marine food variables were associated with plasma concentrations of POPs. This was somewhat expected, as the Norwegian population in general have a high intake of marine food and these foods have been demonstrated to be predictors of POPs in other studies in Norway (Knutsen et al., 2011; Kvalem et al., 2009; Rylander et al., 2009; Sandanger et al., 2006). For instance, of the reported fish variables, boiled cod was a common predictor for the PCBs in the model sample. This might represent a certain dietary pattern in our study

population as Norwegian women with a high intake of boiled cod are more likely to consume fish liver which has a high fat content (> 50%). Accordingly, fresh fish liver has been reported to contain high concentrations of some POPs (Karl et al., 2016; Sandanger et al., 2003). Fatty fish was not identified as an important predictor for any of the POPs in the present study. Indeed, our research group demonstrated in a previous study that intake of fatty fish did not significantly affect the blood burden of POPs in the study group (Rylander et al., 2009). The importance of other foods varied according to compound, and significant food items as cabbage and jam in some of the models, may indicate an underlying dietary pattern associated with increased PCB exposure.

4.5. Strengths and weaknesses

A strength of the present study is the repeated information on sociodemographic and lifestyle variables throughout the period 1991–2005. One example is the information on body weight, which allowed us to assess the impact of weight change over time in relation to POP concentrations at one sample point. Considering that the studied POPs are lipid soluble, half-lives of the different compounds can differ in lean and obese subjects and influence elimination rates (Wolff et al., 2007). It is therefore necessary to adjust for BMI and weight change to optimize regression models. Further, PLS regressions simplified the overview on how different variables were correlated and also minimized the use of multiple statistical comparisons and therefore the probability of wrongly concluding on statistically significant predictors (Gelman et al., 2012).

A weakness of our study may be recall bias, as the information on all variables included in the regression models are based on questionnaires. This may explain some of the discrepancies between measured and predicted POP concentrations as the NOWAC FFQ slightly overestimates fish intake when compared against multiple 24 h recalls (Hjartaker et al., 2007). Further, previous validation studies of FFQs indicate underreporting of total energy intake, especially by obese individuals, whereas healthy food items often are over- reported (Shim et al., 2014). Hence, errors in reported dietary intakes will affect the precision in our prediction models and subsequent misclassification of participants into POP tertiles. There is an on-going debate in the scientific community regarding the ability of FFQs to accurately report individual food intake, where studies report both poor and good validity of FFQs (Archer et al., 2013; Shim et al., 2014; Subar et al., 2015; Yuan et al., 2017; Yuan et al., 2018). However, as described in the method section, the self-reported information in the NOWAC cohort has been thoroughly investigated, and evaluated as good.

Another weakness of our study is that the POP analyses were performed at different laboratories for the two sub-samples. This may explain some of the differences observed in median concentrations of *p,p′*-DDE, PCB-138 and PCB-180 between the model sample and the validation sample. This may further have affected the measure of intermethod agreement for tertile categorization when comparing predicted and measured values. Especially for PCB-138, as the NILU lab included the PCB congener 163 in the quantification of PCB-138 (used in the model sample), which may explain some of the overestimation of PCB-138 concentrations compared to measured concentrations in the validation sample (Centre de Toxicologie de Quebec). Finally, there may be temporal trends in the dietary habits as well as in the sociodemographic variables (especially weight), which makes it difficult to transfer the prediction models to other populations with other dietary patterns, or to younger populations.

4.6. Conclusions

Regression models for predicting concentrations of PCB-153, PCB-180 and summed PCBs, demonstrated moderately good agreement in relation to measured plasma concentrations. The results show that model equations are able to rank individuals according to high, medium and low concentrations. Birth year, breastfeeding history, BMI and weight change were significant predictors for all evaluated POPs, whereas significant dietary predictors varied according to compound. The PCB models can be used to predict PCB exposures in the NOWAC cohort.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The participation was voluntarily and a signed consent was obtained from all the participants. The study was approved by the Regional Committee for Medical Research Ethics (REK, case number: 2015/1780).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.10.057.

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