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Editor's Note: An error was found between advance and final publication. The correction is included before the original manuscript. The error will be corrected in the final published article.

Correction

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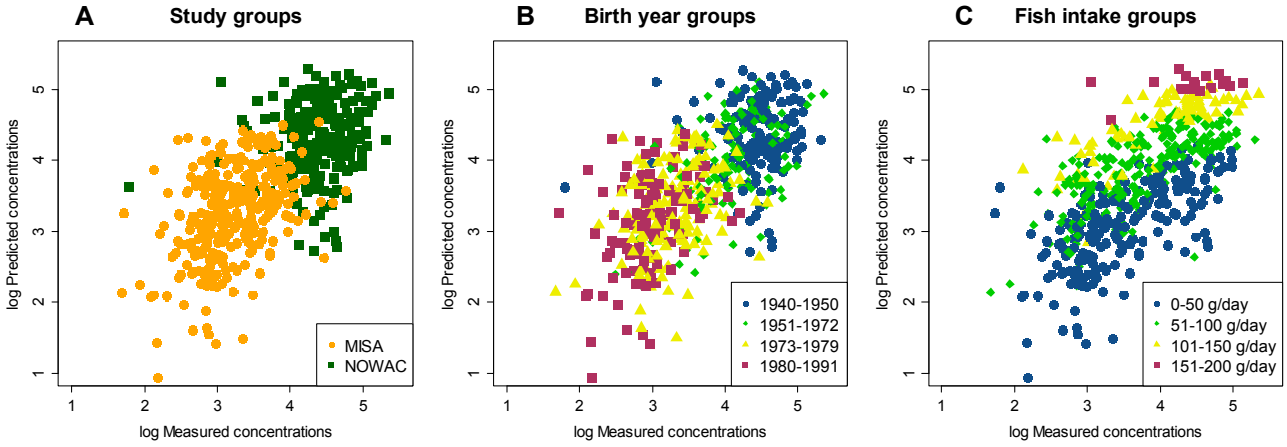
Figure 1 in the Advance Publication showed untransformed concentrations. The revised figure below shows log-transformed concentrations. It will appear in the final published article.



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Estimating Time-Varying PCB Exposures Using Person-Specific Predictions to Supplement Measured Values: A Comparison of Observed and Predicted Values in Two Cohorts of Norwegian Women

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Running title: Individual predictions of PCBs in Norwegian women

Key words: Biomonitoring, Blood serum, Individual PCB predictions, Polychlorinated biphenyls, Time-variant PCB modeling.

Abbreviations: AUC - Area under the curve, DDT - 1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane, LBATs - Longitudinal body burden age-trends, MISA - the Northern

Norway mother-and-child contaminant cohort study, NOWAC - the Norwegian women and cancer study, PCBs - Polychlorinated biphenyls

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Abstract

Background: Studies on 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 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, 2005) 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 regression models including dietary and lifestyle variables and concentrations.

Results: CoZMoMAN accurately reproduced medians and ranges of measured concentrations in the two study groups. Further, rank correlations between measurements and predictions from both CoZMoMAN and regression analyses were 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: The mechanistic model reproduced all measurements of PCB concentrations within a factor of ten and subject ranking and quartile assignments were overall largely consistent, although weak within each study group. Contamination histories for individuals predicted by CoZMoMAN revealed variation between study subjects, particularly in the timing of peak

concentrations. Mechanistic models provide individual PCB exposure metrics that could serve as valuable supplements to measurements.

Introduction

Polychlorinated biphenyls (PCBs) have been detected globally and could potentially be harmful to humans and the environment. Emissions 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. 2011; Verner et al. 2008; 2013). 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 they are linked to historic emissions 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 modeling strategy has also been explored to evaluate PCB exposure time trends in Arctic populations with concurrent transitions in dietary habits (Quinn et al. 2012). Such studies can contribute to formulate and test hypotheses concerning the impact of emission reductions and changes in lifestyle (e.g. diet) 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 were accurate relative to and strongly correlated with measurements and indicate that reliable person-specific predictions are attainable from such models (Verner et al. 2013). To our knowledge, 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 of 4 PCBs from mechanistically derived intake rates. Further, individual LBATs were derived to reconstruct their past exposures. An additional approach using statistical regression analyses of measured PCB concentrations aimed to evaluate the input parameters to CoZMoMAN and identify any dietary or lifestyle predictors not considered within the model.

Material and methods

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 2005. The median (range) age at time of blood sampling of the MISA and the NOWAC women was 30 (18-43) and 56 (48-62) years, 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 and all participants provided informed consent.

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 (g/day) of a range of food items had been calculated from food frequency questionnaires for the MISA (Veyhe et al. 2012) and NOWAC women (Skeie et al. 2006). 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. Some questions were unique to the study groups, e.g. intake of seagull eggs was only included in the MISA study.

Chemical analyses

Concentrations of PCBs in MISA women are reported by Veyhe et al. (2015), 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), which were left in the refrigerator overnight before being extracted through a solid phase extraction 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).

Time-variant model simulations of PCB concentrations

The CoZMoMAN parameterization of the calculation of time-variant PCB contamination of air, water, soil and sediments and of 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 year 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 weight), 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). The input information is summarized in Table 1.

Individual dietary intake rates were calculated from the questionnaire responses asking for consumption of many different food groups during the preceding year. Individual food items were classified as fish, meat or dairy and summed accordingly. Contributions from mixed products were estimated based on percentage content in common brands. The lipid content of meat and dairy food items were obtained from the Norwegian Food Composition Table (Norwegian Food Safety Authority). Wet weight intakes of fish liver (consumed by 101 MISA and 63 NOWAC women) were multiplied by a factor of 50 due to high lipid content (Norwegian National Institute of Nutrition and Seafood Research) relative to the model assumed lipid content of 0.5%, which represents fish muscle (Czub and McLachlan 2004). The summed daily intakes were similar to those described for the study groups in Veyhe et al. (2012) and Rylander et al. (2012). An age-dependent ingestion rate, $I_{default}(X)$, is assumed within CoZMoMAN (Czub and McLachlan 2004 and references therein). As the input intake at 25 years, $I_{individual}(25)$, must be specified as model input, the estimated individual intake rates at time of sampling at age X, $I_{individual}(X)$, was adjusted to age 25 according to Equation 1:

$$I_{individual}(25) = I_{default}(25) \times I_{individual}(X)/I_{default}(X) \quad [1]$$

The reported total months of exclusive and partial breastfeeding for each child was selected to represent the duration of breastfeeding in the simulations. Body weight, metabolic rate and lipid

mass in the women was not described by person-specific information but by the default parameterization (Breivik et al. 2010).

To evaluate the importance of person-specific parameterization of input variables for the predictive ability of CoZMoMAN we performed additional simulations for PCB-153 where individual input values were disregarded and replaced with group median or fixed values for all individuals see Supplemental Material, Table S1).

Data treatment and statistical methods

Statistical analyses were done with R (ver.3.0.0; R Core Team), and statistical significance was defined as $p < 0.05$. Almost all PCB concentrations had lognormal distributions as evaluated by Shapiro-Wilk tests (data not shown).

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, *n*= 116) or to have more than five children (*n*= 8). Further, individuals who stated to "not eat a Norwegian diet on a regular basis" (*n*= 39) or consuming food items that are known to be heavily contaminated (seagull eggs, MISA women only, *n*= 59) that are not considered by CoZMoMAN were also removed.

Predicted and measured concentrations were compared in scatter plots and by Spearman`s rank ($r_s$) and Pearson`s (r_p) correlation coefficients (log-transformed for Pearson`s correlations). Further, measured and predicted values were divided into quartiles and the weighted Cohen`s κ was subsequently calculated as a measure of inter-method agreement 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. To further identify potential influential predictors not accommodated by CoZMoMAN, a statistical approach employing linear regression models examined relationships between all dietary and lifestyle variables (305 and 165 in MISA and NOWAC, respectively) from questionnaires and measured PCB concentrations. Principal component analyses including dietary and lifestyle variables were initially conducted for each study group (results not shown) 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. Estimated concentrations (hereafter referred to as predictions) were derived for each individual from the coefficients in the best fitted models. Further, the agreement between regression predictions and measurements was evaluated in the same way as for the CoZMoMAN predictions.

Results

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

Summary statistics of concentrations of PCBs 118, 138, 153 and 180 are reported in Veyhe et al. (2015) and their medians (range) were 4.0 (<LOD-38), 14 (2.8-118), 25 (5.3-201), 16 (3.0-159) ng/g lipid, respectively. 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, respectively.

Evaluation of agreement between measurements and predictions

Comparisons of concentrations predicted by CoZMoMAN with those measured in MISA and NOWAC women are displayed for PCB-153 in Figure 1A and Table 2, and for PCBs 118, 138, and 180 in Supplemental Material, Figure S1 and Table S2.

Systematic discrepancies of predicted and measured concentrations are evaluated in Figure 1B-C and Supplemental Material, Table S3. The estimated daily fish intakes, birth year, and duration of breastfeeding were associated with discrepancies of CoZMoMAN predictions. Replacing individual values with median daily intakes of meat, fish and dairy products increased correlations from that observed when individual information was used for MISA women; however, this resulted in unrealistically narrow predictions for NOWAC women (Supplemental Material, Figure S2). The correlation to the measured concentrations for all other hypothetical simulations that disregarded individualised parameterization was lower as compared to the main simulation including fully individualised input parameterization (Supplemental Material, Table S1). Also, 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).

Predictions of PCB-153 concentrations from linear regression models

Linear regression models including any significant covariates from questionnaire information were evaluated and the best fitted models explained 36% and 22% of the variation in the measured concentrations (Supplemental Material, Table S4). Birth year and duration of breastfeeding were significant predictors for both study groups. Additionally, body weight and daily 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 (Supplemental Material, Figure S3). Furthermore, median predicted concentrations agreed well with the measured ones: 27.1 and 24.3 ng/g lipid, respectively, for MISA women, and 85.4 and 80.5 ng/g lipid, respectively, for NOWAC women.

Agreements of quartile categorization

Table 3 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. The agreement was stronger for predictions from the regression models as compared to the mechanistic model. Further, the agreement was stronger when results regarded both study groups combined, and better for the MISA group as compared to the NOWAC group.

Individual LBATs

The CoZMoMAN generated estimates of LBATs varied significantly between individuals. Figure 2 illustrates this predicted variability by plotting concentrations obtained from CoZMoMAN from birth until 2010 for 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 3. Rank correlations and scatterplots including the predicted concentrations in the past and at the sampling time as well as with the measurements are presented in Supplemental Material, Figure S4 and

Table S5. These results display that the magnitude of concentrations experienced earlier in life varied between the study groups and that agreement between measurements and predictions was overall best for the MISA group.

Discussion

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. The median age was 26 years older in NOWAC women compared to MISA women at the time of blood sampling (2005 and 2007-2009, respectively), which reflects the difference in median birth years (1949 and 1977, respectively). 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 experienced in the past (Nøst et al. 2013; Quinn and Wania 2012). Different dietary habits between the two study groups likely also contribute to the observed differences (Quinn et al. 2012). Indeed, consumption of marine food items was a predictor of PCBs in these women (Rylander et al. 2012; Veyhe et al. 2015) and MISA women reported to consume less fish compared to the NOWAC women. 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 2005, 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.

Predictive ability of CoZMoMAN for the study groups

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 high for PCB-118 in both study groups and slightly 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 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). Further, the ranges of PCB-153 concentrations generated by CoZMoMAN for the MISA and NOWAC women were similar to the measured ones and demonstrate that CoZMoMAN is able to reproduce realistic concentration ranges in women of different ages and parity.

Person-specific predictions by 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 weak 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). 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 body weight). The stronger correlations of measured and predicted concentrations for MISA women compared to NOWAC women could be related to the range of age in the two groups and differences in internal exposure resulting from

behaviours in the past related to PCB exposure or elimination. Also, the former originate from Northern Norway whereas the latter from all of Norway and the CoZMoMAN predictions for the PCB content in fish may be more representative for Northern Norway.

The prediction errors were largely explained by daily intakes of fish, birth year and total duration of breastfeeding (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 S2). The stronger correlation for MISA women could imply that although simulations depend on the dietary intake of fish, this input variable also introduces some misreporting in individual questionnaires into predictions. Still, the food frequency questionnaires are considered of good quality and calculated dietary intake estimations are realistic (Rylander et al. 2012; Totland et al. 2012; Veyhe et al. 2012). Discrepancies of predicted concentrations were also associated with the breastfeeding variable (Supplemental Material, Table S3); however, correlations to measured concentrations were better for women who had children than for nulliparous women. Taken together this implies that individual parameterization of each input variable is necessary to create contrasts in predicted concentrations although the input information likely also contributes to the uncertainty in model predictions.

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 1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane (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 parameterized 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 parameterization is not feasible.

Concentration predictors in regression analyses

Regression models were intended to identify predictors not accounted for by CoZMoMAN and the best fitted regression models for 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 S4). Multivariate analyses in MISA women indicated age, parity, body mass index and dietary intakes of freshwater fish, fat fish, fish liver and reindeer as significant predictors (Veyhe et al. 2015). 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 a predictor of concentrations in these women (Veyhe et al. 2015) 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 only borderline significant for the NOWAC women.

Summarizing person-specific predictions

Our evaluation of predictions suggests that a priori estimates of person-specific PCB-153 concentrations from CoZMoMAN 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 κ>0.6) for both study groups. Rank correlations between measurements and predictions were strong only when MISA and NOWAC women were regarded collectively demonstrating that the model performs better when the targeted study groups include a wider range of personal characteristics (e.g. includes older and younger persons) as input information and thus also considers a wider spread in concentrations.

It is important to note that the main predictors for measured PCB concentrations indicated by statistical approaches were mechanistically accounted for by CoZMoMAN. Still, although fish intake was a predictor of PCB concentrations, CoZMoMAN attributes too much of the inter-individual differences to variable fish intakes. Also, there is still individual variation not explicitly addressed in CoZMoMAN nor identified in statistical analyses of the information in questionnaires.

Person-specific prediction of PCB concentrations has 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 Inuit adults (Sonne et al. 2014); and ii), a toxicokinetic model predicting three measurements throughout early childhood (Verner et al. 2013).

In this study, agreement between measured and predicted concentrations was better for predictions based on regression models compared to from CoZMoMAN; however, this was expected as regression models are constructed from the measurements themselves. The mechanistic modeling has the advantage that it (i) does not rely on measured concentrations as input and (ii) can avoid pitfalls of statistical approaches in terms of causal relationships. From a modeling perspective, the attainment of all predicted concentrations within a factor of ten of measured concentrations and acceptable overall ranking of persons is remarkable and lend further support for mechanistic modeling approaches. We believe there is significant scientific and regulatory merit in mechanistically assessing the impact of changes in emissions for internal exposure at the individual level and across time. Nevertheless, our comparison between statistical and mechanistic approaches also identified exposure pathways of significance to some individuals which the latter is ignoring (e.g. consumption of seagull eggs). As the model is parameterized for a specific region, further refinements may also be required before it can be applied to other areas (e.g. Quinn et al. 2012).

Single measurements and predicted LBATs

The time-resolved feature of CoZMoMAN allows for an expanded understanding of individual exposures with regards to predicting LBATs that provide important perspectives on internal exposure on an individual basis. Figures 2 and 3 clearly show 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 exposure measures for effect-related studies. Indeed, point estimates of concentrations at birth, 10 years of age and at 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 (Supplemental Material, Table S5). 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 concentrations at the time of sampling appear 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 across almost thirty years 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 the older NOWAC women occurred when they were adults whereas the younger 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 (indicated as N1 and N3 in Figure 2) whereas breastfeeding in the 1980s caused concentrations in those older mothers to

drop significantly (N2 and N4 in Figure 2). Breastfeeding also lowered concentrations in MISA women (M6 and M7 in Figure 2) and changed the individual ranking of predicted PCB burdens in MISA women at the time of sampling (consider M6 and M7 relative to M5 in Figure 2). 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).

Conclusions

The CoZMoMAN model was able to reproduce group medians and ranges of PCB concentrations in pregnant and postmenopausal Norwegian women. Furthermore, ranking of individuals based on predictions and measurements were largely consistent, although weak when both study groups were regarded separately.

Predicted LBATs derived from CoZMoMAN suggested large differences in past concentrations experienced by the MISA and NOWAC women. Mechanistic modeling provides information of individual concentrations through life that is valuable as well as useful supplements to exposure characterization in cross-sectional PCB measurements.

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.

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.

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.

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].

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.

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.

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.

R Core Team. 2013. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available: http://www.R-project.org/. [accessed 25 April 2013].

Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbühler K. 2011. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the united kingdom. Environ Health Perspect 119(2):225-231.

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. 2008. 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 71:18644.

Veyhe, AS, Hofoss, D, Hansen, S, Thomassen, Y, Sandanger, TM, Odland, JØ, Nieboer, E. In press. The Northern Norway mother-and-child contaminant cohort (MISA) study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy. Int J Hyg Envir Heal 218(2):254-264.

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.

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

Table 2: The median predicted concentrations of PCB-153 (ng/g lipid) and their discrepancy, ratio and correlations to measured concentrations.

Study group	Median prediction	Median discrepancy	Median ratio (range)	Correlation r_s	Correlation r_p[a]
MISA	28.8	+4.8	1.06 (0.16-6.44)	0.40**	0.41**
NOWAC	78.2	-3.3	0.94 (0.16-7.92)	0.13**	0.14*
Both combined	-	-	-	0.67**	0.67**

*p<0.05, **p<0.001 [a]r_p calculated for log-transformed concentrations.

Table 3: Agreement in quartile categorization based on predictions obtained from CoZMoMAN and linear regressions compared to the measured concentrations in MISA and NOWAC women.

	Correct quartile n (%)			Weighted Cohen`s κ		
Approach	**MISA**	**NOWAC**	**Combined**	**MISA**	**NOWAC**	**Combined**
Mechanistic modeling	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

Figure legends

Figure 1: Measured serum concentrations of PCB-153 along with those predicted (both in ng/g lipid) by CoZMoMAN for the MISA (*n*=310) and NOWAC (*n*=244) study subjects in groups according to their study group (A), birth year (B), and their daily intake of fish (C).

Figure 2: 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 2005. 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.

Figure 3: Person-specific predictions of concentrations of PCB-153 at birth (A), at 10 years of age (B), of cumulative concentrations (product of concentration across time) during puberty (age 11-16 years) (C), and of concentrations at age of first child birth (D) are displayed separately for the two study groups. Boxes extend from the 25th to the 75th percentile, horizontal bars represent the median, whiskers extend 1.5 times the length of the interquartile range (IQR) above and below the 75th and 25th percentiles, respectively, and outliers are represented as points.

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Figure 1.

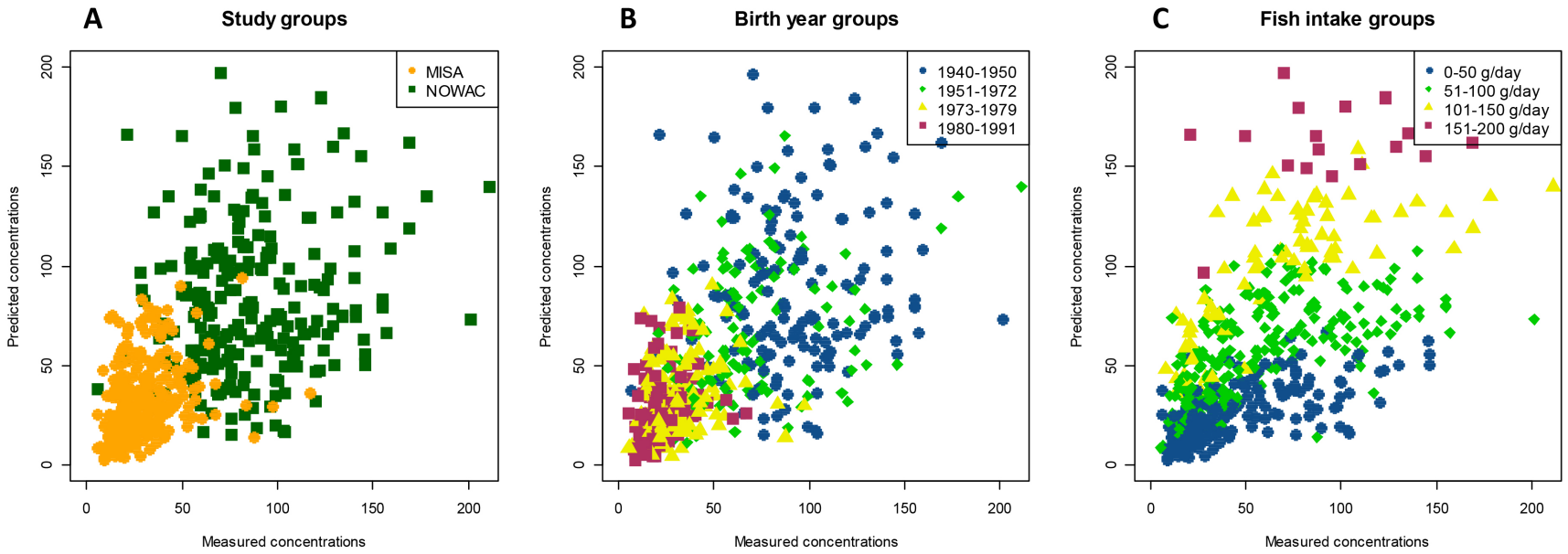

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Figure 2.

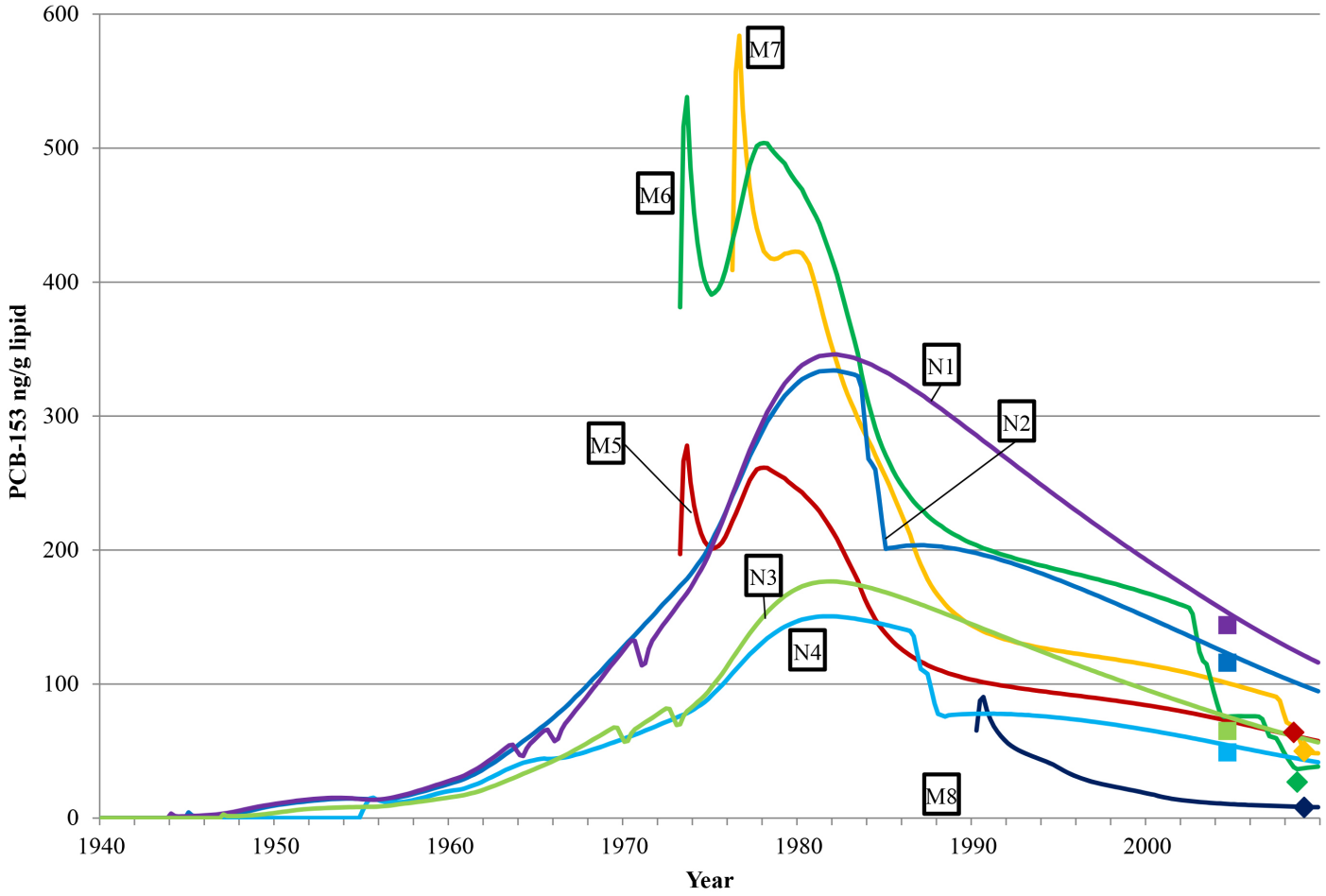

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Figure 3.