Mechanistic Modelling in Support of Human Biomonitoring

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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Abstract

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Lifetime exposures to polychlorinated biphenyls (PCBs) were calculated using a combined mechanistic model of environmental fate (BETR-Global) and human food chain bioaccumulation (ACC-Human) for 6128 participants of the United States National Health and Nutrition Examination Survey (NHANES) 1999-2004. Important questionnaire information from NHANES (year of birth, diet, body mass index (BMI), sex, reproductive behaviour) were used as model input. The model performed well on a population level, where the geometric mean modelled concentration of 13.3 ng/g lipid is close to the geometric mean measured concentration of 22.0 ng/g lipid. While the model successfully reproduced measured trends with age, sex, BMI, a failure was observed with diet. Furthermore, the model was used to explore the relationship between PCB levels and BMI, and it was found that these relationships depend on i) age, ii) the time of sampling, and iii) the range of body mass index sampled.
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Chapter 1

Bioaccumulation, Biomonitoring, and Exposure Modelling in Humans: An Overview

1.1 Bioaccumulation

Bioaccumulation is the process that leads to higher levels of environmental contaminants in an organism relative to the organism’s surrounding environment. [1,2] This is usually caused by the uptake rate of the contaminant being faster than the rate at which the contaminant is eliminated from the organism. [2]

Bioaccumulation is governed by certain physicochemical properties - namely the chemical’s preference for the lipid phase. In other words, bioaccumulation can be a function of partitioning. To estimate this preference for the lipid phase, often n-octanol is used as a surrogate for lipids; this allows for an equilibrium partition coefficient to be defined: the octanol-water partition coefficient ($K_{OW}$)

$$\log_{10} K_{OW} = \log_{10} \left( \frac{C_{\text{octanol}}}{C_{\text{water}}} \right) \quad (1.1)$$

For this work, the use of n-octanol as a surrogate for lipids forms the basis for describing the capacity of an organism to take up contaminants.
This thesis examines a group of bioaccumulating contaminants known as persistent organic pollutants (POPs), in particular polychlorinated biphenyls (PCBs). Most work presented in the thesis focuses on 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153), a biphenyl with 6 chlorine atoms attached, shown in Figure 1.1 below.

![Chemical structure for PCB-153](image)

Figure 1.1: Chemical structure for PCB-153

### 1.2 Human Biomonitoring

Human biomonitoring (HBM) studies are designed primarily to i) identify what contaminants a population is exposed to, ii) quantify the level of these exposures, and iii) with repeated sampling over time, identify how a population’s exposure to a particular contaminant is changing. [3] Typically, these studies involve the collection of blood, urine, or other biological tissues for analysis of environmental contaminants.

The work in this thesis focuses on one prominent national biomonitoring campaign: the United States National Health and Nutrition Examination Survey (NHANES). [4] NHANES is conducted on a continuous basis and represents a stratified multistage probability sample of the civilian non-institutionalized population of the United States. [4] Like most biomonitoring campaigns, NHANES includes an extensive questionnaire with information on, but not limited to, diet, general health, reproductive health, demographics, and medical conditions.

The biomonitoring data collected in NHANES, particularly data on PCBs, displays considerable variability (Figure 1.2). Often, and certainly in the higher chlorinated congeners, the range of measured levels exceeds $2 \log_{10}$ units, sometimes reaching $3 \log_{10}$ units. It is of considerable interest to explain this variability and identify what factors, e.g., age, body mass index (BMI), sex, are most responsible for the differences in PCB levels. Typically, statistical analysis is used to identify associations between PCB body burden and these factors. [5–11]
Figure 1.2: Box and whisker plots of lipid adjusted, log$_{10}$ PCB concentration for congeners 28, 52, 101, 118, 138, 153, and 180 for participants of NHANES 2003-2004. The solid horizontal line in the box indicates the median. The bottom and top of the box indicates the 25th and 75th percentile, respectively. The ends of the whiskers represent the point closest to 1.5 times the interquartile range (IQR).

1.3 Human Exposure Modelling

1.3.1 Mechanistic Exposure Models

By integrating models of environmental fate and food chain bioaccumulation we now have the capability to mechanistically describe the journey of POPs from their initial release into the physical environment to their accumulation in top predators, including humans. [12,13] A particularly important feature of this approach is its dynamic nature, which allows for simulations of time-variant chemical emissions covering periods of multiple decades. This approach was first detailed by Breivik et al. [12] using a model named CoZMoMAN, which combined the previously developed coastal-zone model for POPs, CoZMo-POP 2 developed by Wania et al. [14] and the human food chain bioaccumulation model ACC-Human developed by Czub and McLachlan. [15] The combined model was successful at predicting concentrations in various biota and environmental media. [12]

Following this approach, Quinn et al. [13] used the CoZMoMAN model to investigate the effect of a mother’s reproductive behaviours on human PCB exposure. These reproductive behaviours included:
mother’s age at childbearing, number of children born, and whether or not the infant was breastfed versus receiving formula milk. Quinn et al. sought to evaluate the effects of these behaviours using three key metrics: prenatal PCB exposure, postnatal PCB exposure, and lifetime PCB exposure. The model results indicated that a mother’s reproductive history - how many children they had - had a greater effect on their child’s prenatal and postnatal exposure than on their own cumulative lifetime exposure to PCBs. Additionally, a child’s order of birth is the largest factor that affects prenatal exposure. Successively born children had lower prenatal exposures than the child before them. This holds true for scenarios involving constant emissions over time as well as non-steady-state emissions.

Another study by Quinn and Wania [16] investigated the relationship between PCB body burden and age, again using the integrated mechanistic model CoZMoMAN. Quinn and Wania identified that previous studies that found a positive relationship between PCB levels [17, 18] and age had incorrectly associated that older age results in higher PCB exposure. In fact, the observed cross-sectional body burden versus age trend, or CBAT, depends on whether the biomonitoring measurements were taken during periods of increasing or decreasing emissions, as well as the human biotransformation half-life of the contaminant. [16] Essentially, in a post-ban scenario where emissions are declining, and thus environmental levels are declining, older age is associated with higher PCB levels because those individuals had lived during the peak in PCB emissions and exposure.

On the other hand, simpler toxicokinetic models also seek to mechanistically estimate time-variant POP concentrations in humans by way of using information on intake rates (which requires information on POP levels in the diet), distribution, and elimination kinetics (e.g., biotransformation, fecal egestion, urinary excretion). [19, 20] However, such models lack the ability to fully describe the link between emissions of a contaminant and levels in humans, as shown previously.

1.3.2 Combining Human Biomonitoring and Deterministic Modelling

Recent work by Ritter et al., [20, 21] Wong et al., [22, 23] Gyalpo et al., [24] have all tied human biomonitoring data together with pharmacokinetic models to extract relevant parameters. For example, Gyalpo et al. back-calculated chemical uptake rates of polybrominated diphenyl ethers (PBDEs) in the Australian population. [24] Ritter et al. estimated intrinsic elimination half-lives for various PCB congeners using biomonitoring data from the United Kingdom. [21] Wong et al. used biomonitoring
data from North American populations to estimate both uptake rates and intrinsic elimination rates for PBDEs. [23]

In this thesis, a more ambitious approach to link biomonitoring data and mechanistic exposure models is sought. The goal is to combine a global mechanistic model of environmental fate and transport, BETR-Global, [25] with the mechanistic food chain bioaccumulation model ACC-Human. [15] The combined model approach was applied on an unprecedented scale to calculate the lifetime PCB exposure in over 6000 individual participants of NHANES 1999-2004.

1.4 Objective and Structure of Thesis

This thesis examines a few important questions:

1. Can a combined model of contaminant environmental fate (using information on PCB emissions to the environment beginning in 1930) and human food chain bioaccumulation accurately predict PCB levels for participants in a national biomonitoring campaign?

2. What factors contribute most to the variability observed in human biomonitoring campaigns?

3. Can the model accurately reproduce trends observed in the biomonitoring data with factors such as age and diet?

4. If not, what are the reasons for failure?

5. What can a mechanistic model tell us about the relationship between body mass index and PCB levels?

6. What factors may influence the observed trends between PCB levels and body mass index?

Chapter 2 explores the application of a combined mechanistic model of environmental fate and human food chain bioaccumulation to reproduce PCB levels in over 6000 participants of a national biomonitoring campaign. It further investigates whether the model reproduces trends with key factors such as age, diet, and sex. It also investigates the reasons for why the model succeeds with capturing these trends for some factors, but fails for others.
Chapter 1. Introduction

Chapter 3 examines the role of body mass index and how it influences PCB levels in humans. Quite often, biomonitoring data displays diverging relationships between PCB levels and body mass index (positive, negative, or no relation). Therefore, the goal of the work presented in this chapter was to use a mechanistic bioaccumulation model to provide a mechanistic understanding of these relationships and identify what key factors (such as age, time of sampling) influence the observed relationship between body mass index and PCB levels.
Chapter 2

Deterministic Modelling of the Exposure of Individual Participants in the National Health and Nutrition Examination Survey (NHANES) to Polychlorinated Biphenyls


Contributions: The model(s) used for this research project was previously developed and published by G. Czub and M. MacLeod. Modelling assistance was provided to S. Wood by M.J. Binnington and J.M. Armitage. S. Wood ran the model, interpreted model output, wrote the manuscript, revised it, and responded to reviewer’s comments under the guidance of F. Wania.
2.1 Introduction

Polychlorinated biphenyls (PCBs) are a class of persistent organic pollutants (POPs). They have a variety of industrial uses, e.g., as coolants in electrical transformers, sealants, and insulating fluids. In the United States, PCBs were first produced in 1929, and due to their potentially harmful effects on wildlife and humans, their production (and import) was prohibited in 1979. [26] The predominant source of exposure for the general population is the ingestion of PCB contaminated food stuffs, particularly fish and livestock. [27, 28] Adverse health outcomes stemming from PCB exposure are of particular concern; for example, some evidence has been found of associations between PCB serum levels and diabetes, [29–31] hypertension, [32,33] and endocrine disruption. [34,35]

Human biomonitoring (HBM) studies involve the collection of blood, urine, or other tissues for analysis of environmental contaminants. These studies aim to identify which environmental contaminants a population is exposed to, and quantify the level of these exposures. [3] With repeated sampling over time, HBM studies can also provide insight on how a population’s exposure to a contaminant is changing. One prominent example is the United States National Health and Nutrition Examination Survey (NHANES). NHANES represents a stratified multistage probability sample of the civilian non-institutionalized population of the United States. It is conducted on a continuous basis and includes an extensive questionnaire with information on diet, health, and demographics. [4] Blood and urine samples are collected and analyzed for a suite of organic chemicals. The biomonitoring results in NHANES includes data on many POPs such as PCBs, polybrominated diphenyl ethers (PBDEs), and pesticides, e.g., hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (DDT). [36,37]

Measured PCB concentrations from HBM studies often vary widely; for example, 2003-2004 NHANES PCB-153 levels range from 1.05 ng/g lipid to 986 ng/g lipid across the analyzed serum samples. Thus, it is of interest to ascertain the extent to which various factors - age, dietary composition, sex, body mass index (BMI), etc. - contribute to differences in levels. Traditionally, this has been accomplished by identifying statistical associations between measured contaminant body burdens and these factors. In non-occupationally exposed populations age, sex, and BMI have been shown to significantly associate with PCB body burdens. [5–11] Age is frequently positively associated with PCB body burden. [9,36,37] Generally, the male sex is associated with higher PCB levels, [7] while associations between BMI and PCB body burden are inconsistent. [38–40]

Statistical associations do not necessarily imply causal relationships and thus provide limited mechanistic insight into the sources of variability in contaminant levels. They are also generally not suited
for making predictions. Toxicokinetic models of varying complexity that mechanistically estimate time-variant POP concentrations in humans [19,20,41,42] constitute a complementary approach to statistical methods. In these models, POP concentrations in humans are calculated using information on intake rates, distribution, and elimination kinetics (e.g., biotransformation half-life). These calculations generally require time-variant POP intakes as an input parameter. More ambitious approaches seek to also predict intakes by calculating the transfer of POPs through the food chains leading to humans (e.g., ACC-Human). [15] If such human food chain models are further combined with mechanistic models of chemical fate in the physical environment (e.g., CoZMo-POP 2 [14]), integrated models can mechanistically describe the journey of POPs from their initial release into the environment to their accumulation in humans; CoZMoMAN is one model example, [12] which has been used previously to simulate human exposure to PCBs for different purposes. [13,16,43–45] A particularly important feature of such an approach is its dynamic nature, which allows for simulations of time-variant chemical emissions covering multiple decades. Because such emission estimates are available for PCBs, [46] the application of integrated models has focused on these chemicals.

In the present study, we combine a global-scale fate model with a human food chain bioaccumulation model to predict the exposure of Americans to PCBs. Specifically, we use time-variant global emissions of PCBs, to mechanistically quantify their global fate and transport, and transfer through aquatic and agricultural food chains, in order to predict the concentration of four PCB congeners during the entire life of 1999-2004 NHANES participants. By comparing individual predicted PCB concentrations (at time of sampling) to measured PCB levels, this approach utilizes a large, high quality, and diverse empirical dataset (wide age range, both sexes) to perform a novel model evaluation. It also allows for an assessment of different aspects of model performance, including our ability to accurately predict (i) individual contaminant levels, (ii) the mean and range of total population contaminant levels, and (iii) the relationship between contaminant levels and certain demographic factors (age, diet, sex, BMI). The results of such an evaluation should then be able to inform what aspects of the model prediction need improvement, and how the model can be applied with confidence.
2.2 Methods

2.2.1 Modelling overview and summary

We aim to simulate human exposure to PCBs at both the population level (average) and on an individual basis. Figure 2.1 illustrates the modeling approach used to simulate PCB exposures of individual NHANES participants. Since the diet represents the main source of general population PCB exposure, and the intrinsic elimination half-lives of some PCBs in humans exceed a decade, the calculation of historical PCB levels in foodstuffs is required. We focused on PCB congeners 118, 138, 153, and 180, because of their well-defined physical-chemical properties, historical emissions, and frequent detection within NHANES. Starting with historical emissions (Fig. 2.1A), the global-scale fate model is used to calculate the ambient concentrations of these four PCBs in the United States over time (Fig. 2.1B). These concentrations serve as input to the human food chain bioaccumulation model (Fig. 2.1C&D), which outputs concentration as a function of time for the various organisms in the model assumed to constitute the human diet (e.g., fish, beef, dairy, Fig. 2.1E). Air, freshwater, and food item PCB concentrations (Figure 2.1B, E) are then combined with individualized human demographic input data to derive longitudinal time trends of PCB exposure for each individual (Fig. 2.1F). Finally, the concentration at the time the individual was sampled is compared with the measured concentration reported in NHANES (n = 6128, Fig. 2.1G). Population level PCB concentrations are obtained by averaging the results of modeled individuals.

2.2.2 Prediction of PCB concentrations in air, water and soil

Concentrations in the physical environment are calculated using BETR-Global, which is a dynamic, fugacity-based, global scale environmental fate and transport model. [25] It separates the physical world into 288 cells based on a 15 longitude by 15 latitude grid. Each cell is composed of seven environmental compartments: upper air, lower air, vegetation, freshwater, soil, coastal water, and sediment. Contaminants are allowed to transfer between compartments and between neighbouring cells. The model requires information on a contaminant’s physical-chemical properties, e.g., the octanol-water partition coefficient $K_{OW}$ and the air-water partition coefficient $K_{AW}$, environmental degradation half-lives, and historical time-variant emissions (Fig. 2.1A); PCB emission data are from Breivik et al. [46] A complete description of input properties can be found in the Supporting Information, Table 2.1. Because of the
long residence time of PCBs in the environment, global PCB fate and transport is simulated from the beginning of PCB production in 1930 [26] until 2010.

### 2.2.3 Prediction of PCB concentrations in food

The dynamic, fugacity-based, mechanistic bioaccumulation model ACC-Human [15] is used to describe the uptake of POPs in the human food chain from concentrations in air, water, and soil. It includes an aquatic food chain (Fig. 2.1C, consisting of zooplankton, planktivorous fish, and piscivorous fish) and an agricultural food chain (Fig. 2.1D, consisting of grass, milk cows, and beef cattle). Dietary intake of PCBs is assumed to occur through the consumption of three dietary items only (beef, fish, and dairy products). Dietary intake of PCBs from other foodstuffs is either deemed negligible (e.g., plant based food [47]) or is represented by one of the three (e.g., fowl, pork is represented by beef, Supporting Information, Table 2.3). The latter is based on lipid-adjusted PCB concentrations in different meats that are generally within a factor of 2 of each other (see Supporting Information, Table 2.8).

The PCB concentration calculated for coastal water in cell 76 of BETR-Global, corresponding to the Pacific Ocean adjacent to the California coast, is the basis for the aquatic food chain calculations in ACC-Human, whereas the PCB levels in air, fresh water, and soil in cell 78, corresponding to the central United States, are inputs for the agricultural food chain calculation. There are several assumptions inherent to this approach. Due to the lack of geographical information (i.e., no information on the source of food or geographical location of NHANES participants), the contamination of all foodstuffs is based on the environmental contamination of the atmosphere over the central United States (for the agricultural food chain) and in the seawater off the west coast (for the aquatic food chain). In other words, there is no regional differentiation in the food supply, and the food sources are the same for Americans everywhere. Modelled air concentrations in other regions of the United States were generally within a factor of 2 of the modelled air concentrations in the central United States, suggesting that regional differences in food chain contamination may be relatively minor. Our approach also ignores changes in food production over the entire simulation time period (1930-2010), for example, the transition from locally produced food and livestock to a nationally integrated food industry, and the transition from grass-fed to corn-fed beef. Additional modeling indicated that PCB levels in grass and corn are similar (i.e., within a factor of 1.5) (data not shown). Additionally, dietary transitions on the population level are also ignored (e.g., the shift to leaner meats). [48]
Figure 2.1: Graphical overview of the modelling approach.
2.2.4 Prediction of PCB concentrations in individual humans

The human sub-model within ACC-Human [15] is used to calculate the concentration of the four PCB congeners in each NHANES 1999-2004 participant (n = 6128) at their time of sampling. Because of the long residence time of PCBs in humans, this requires the calculation of each participant’s lifetime exposure history. Input parameters that are adjusted for each study participant using information extracted from their NHANES questionnaire include year of birth, sex, BMI, the dietary intake of fish, beef lipids and dairy lipids, and - in the case of mothers - number of children, mother’s age at each childbirth, and nursing duration(s) (for a summary of input parameters, see Supporting Information, Table 2.2). In brief, the ACC-Human model calculates PCB levels in humans by considering uptake from the diet, inhalation, and drinking water, and also the elimination of the contaminant by fecal egestion, biotransformation and skin shedding, and in the case of mothers, childbirth and nursing. To arrive at a lipid-normalized concentration, the total mass of chemical in the human body is divided by the total lipid mass of the human, which is a function of age, sex, and BMI.

Breastfeeding is parameterized as follows: mothers who responded “Yes”, “Don’t know” or did not respond to the question “Breastfed any of your children?” are assumed to have breastfed all children for 6 months (as recommended by the American Academy of Pediatrics). [49] Participants who responded “no” did not breastfeed any of their children. All participants are assumed to have been breastfed in their infancy. Exposure from breastfeeding is unlikely to have a significant impact on the model concentrations, as the minimum participant age in the NHANES PCB biomonitoring data is 12 years.

Because PCBs are associated mostly with lipids within the body differences in the lipid content of study participants could be a source of concentration variability. [50] In order to account for the wide range in lipid contents, we modified the original ACC-Human model to allow the user to assign each study participant to one of 22 BMI (from BMI = 17 to 38 kg/m\(^2\), in increments of 1). For each BMI, a growth curve is defined which determined the change in lipid content with age. Details on these lipid weight and body weight growth curves can be found in the Supporting Information, Section 2.5.3.

Each individual’s intake of beef lipids and dairy lipids is estimated using responses from a 24-hour dietary recall interview on individual foods. [4] Fish intake is estimated using a food frequency questionnaire (FFQ) on fish consumption. [4] Each individual is assumed to eat the same diet throughout his or her entire lifetime, with a consistent composition based on their dietary recall. On average, the dietary intake values derived from the NHANES data are approximately 1.5 times lower than average American
food consumption reported in the USDA Agriculture Fact Book. Because of the potential for dietary intake underreporting to influence estimated PCB exposures, a scaling factor is implemented for each food item to bring the NHANES average diet in line with the USDA average. The scaling factors applied to all individuals are approximately 1.5 for beef and dairy lipids, and approximately 2 for fish. The application of scaling factors requires the assumption that the PCB biomonitoring subsample of the NHANES population is identical to the US population, i.e., we did not take into account the sampling weights assigned to each NHANES participant. A full description of the process used to convert the dietary questionnaire information into daily intake rates of fish, beef, and dairy can be found in the Supporting Information, Section 2.5.4. The possibility to specify an individualized BMI/growth curve and individualized diet represent a significant expansion in the capabilities of the ACC-Human model, which previously allowed for only a single growth curve and diet for each gender.

Humans additionally take up PCBs by inhaling air and drinking water. These exposures are calculated using the concentrations in lower air and fresh water, respectively, from cell 78 of BETR-Global, i.e., all Americans are assumed to inhale air and drink water from the central USA. Although environmental contamination in air and freshwater may be greater in other parts of the US (e.g., the East coast and urban locations), exposure of the four PCB congeners from inhalation and drinking water is insignificant compared to exposure from dietary intake. For the same reason, the inhalation rate (15 m$^3$/d) and water consumption rate (3 L/d) are not individualized. Other, non-individualized model input parameters include the human biotransformation half-life ($H_{lb}$) for PCBs and the body lipid excretion rate (i.e., skin shedding, 0.8 g lipid/d).

Our approach assumes that exposure only occurs through far-field sources, i.e., from general environmental contamination and not from occupational or indoor exposure. Since dietary lipid intake is the main source of PCB exposure to the general American population, or representative NHANES sampling target, this assumption is appropriate.

While the geographic location of NHANES participants is confidential, reported regional differences in human PCB concentrations are minor: the geometric mean concentration was only 1.4 times greater for people living in the Northeastern US than elsewhere in the nation. While this justifies our approach of using the output of a single BETR-Global cell as the input for the food chain calculations, we also explored with our modeling approach the extent of regional concentration differences that could be expected if American diet were sourced regionally. By varying the BETR-Global cells chosen to drive contamination in the food chain, we predict regional geographic differences in human PCB-153
concentrations of at most a factor of two compared to our reference calculations (data not shown). This is larger than the differences reported by Wattigney et al., [54] which can be explained by the fact that the diet of most Americans will include items sourced from outside their region of residence.

2.2.5 Constraining emissions timing and human biotransformation half-life

The emission history, in particular the time of peak emissions (E(t)), and the human biotransformation half-life (HLb) are uncertain model input parameters, yet can have a strong impact on the relationship between PCB body burden and age for a population cross-section. [16, 20] Furthermore, Breivik et al. [12] has previously stated that the emissions of PCBs prior to 1980 are potentially underestimated. However, it is difficult to assess the potential bias in emission estimates for this period because of the lack of monitoring data for PCBs in abiotic media and biotic tissues prior to 1970. [12]

As a preliminary exploration, we developed an algorithm to optimize the selection of E(t) and HLb values for the PCBs simulated here. Specifically, three different emissions scenarios (the default emission inventory from Breivik et al., [46] or peak in emissions occurring 5 or 10 years earlier) were combined with HLb values ranging from 1 to 300 years (every 1 year between 1 and 30, and every 10 thereafter) to yield the smallest sum of squared residuals (SSR) between the modeled concentrations of PCB congeners 118, 138, 153, and 180, and the measured concentrations reported for NHANES participants. Data from 6 years of NHANES (2003-04, 2001-02, and 1999-2000) were considered. The use of multiple NHANES years, combined with data on four congeners, provided us confidence in the validity of this fitting procedure. The implication here is that the model is being refined to generate data that best fit the measured data. However, as mentioned previously, these major input parameters are uncertain and we confirmed that the values obtained for E(t) and HLb are within the plausible range. Further details can be found in the Supporting Information, Section S5. We note that this optimization procedure is similar to the use of HBM data in the derivation of intrinsic human elimination half-lives as described by Ritter et al. [21] However, here only the biotransformation half-life is optimized. The overall intrinsic elimination half-life is still influenced by other depuration processes (e.g., fecal egestion, breastfeeding) and hence varies according to the related input parameters (e.g., BMI/lipid content, reproductive history).

2.2.6 Data visualization, statistical methods, and other software

All statistical and data analysis were performed using R (version 3.1.3) and Python (version 2.7.7) [55] with additional libraries NumPy (ver. 1.8.1) [56], SciPy (ver. 0.14.0), and pandas (ver. 0.14.0) [57].
Additionally, all graphical representations of data were generated using matplotlib (ver. 1.3.1) [58]. Associations between PCB-153 exposure (modeled and measured values) and model input parameters were assessed using linear regression.

2.3 Results

2.3.1 Optimized emission history and human biotransformation half-life.

For all congeners (118, 138, 153, and 180), assuming that the peak in emissions occurred 10 years earlier than reported in Breivik et al. [46] results in the lowest SSR, i.e. the best fit between model and measurement requires a shift in peak emissions from 1970 to 1960. While this shift is not derived mechanistically, it is not unreasonable. Whereas production of PCBs peaked in the 1970s, it is possible that emissions of PCBs were higher in the previous decade (e.g., due to industrial emission not accounted in Breivik et al. [46] or emission factors that were higher before the problematic nature of PCBs became obvious). [12] We consider this emission time shift only a preliminary hypothesis and suggest that the historical emission history of PCBs should be revisited to find a rigorous mechanistic explanation for higher emissions in the past. Such an effort is considered outside the scope of the current study however.

The optimized HL\textsubscript{b} values for PCB congeners 118, 138, 153, and 180 are 8, 25, 35, and 300 years, respectively. In order to compare these results with those reported in the literature, we used the HL\textsubscript{b} to estimate intrinsic elimination half-lives: 2 to 7 y for PCB-118, 2 to 18 y for PCB-138, 3 to 24 y for PCB-153, and 3 y to 50 y for PCB-180 (values range depending on sex, age, and BMI, for details see Supporting Information, Figure 2.14). Our estimates compare favorably with those calculated by Ritter et al. [21]: 9.3, 10.8, 14.4 and 11.5 y for PCB-118, 138, 153, and 180, respectively, and Aylward et al. [59]: 5, 11, 14.4, and >20 y for PCB-118, 138, 153, and 180, respectively. Considering the large uncertainty of HL\textsubscript{b}, the optimized values obtained here do not deviate unreasonably from earlier estimates. [16] In particular, the differences in the HL\textsubscript{b} values between the four congeners conform to expectations. All results presented below are based on these optimized emission history and biotransformation half-lives.
2.3.2 Comparison of model predictions and measured data at the population level

Figure 2.2A compares predicted and measured PCB-153 concentrations at the population level for the original and revised emission scenario (i.e., $E(t) = 1970$ and $E(t) = 1960$). In general, for the optimized scenario, the model slightly underestimates PCB-153 levels when compared to the measured data. The geometric mean modeled concentration of 13.3 ng/g lipid is close to the geometric mean measured concentration of 22.0 ng/g lipid. Similar agreement is found when comparing median concentrations, where the modeled value of 15.7 ng/g lipid is somewhat lower than the median measured concentration of 22.2 ng/g lipid. Similar results are observed for the other PCB congeners, see Supporting Information, Table 2.4, and Figures 2.8, 2.9, 2.10). This level of agreement is quite remarkable, considering the complexity of the model approach, the number of required assumptions, and the uncertainty of many input parameters. The default emission scenario ($E(t) = 1970$; default 15 y biotransformation half-life for PCB-153) also performs well: the geometric mean measured concentration of 19.2 ng/g lipid is very similar to the geometric mean measured concentration of 22.0 ng/g lipid. However, model results based on the default/original scenario fail to reproduce trends with age ($R^2 = 0.04$), a very important predictor of PCB level. Predicted concentrations in younger individuals (Age Class 12 - 15 y, 16 - 24 y) tend to overestimate the empirical data whereas predicted concentrations in older individuals (Age Class 42 - 61 y, 61 - 85) tend to underestimate the empirical data. See Supporting Information, Figure 2.7 for a comparison of the default/original model results and measured levels.

The range of predicted concentrations (6 log$_{10}$ units, 0.001 to 598 ng/g lipid) is much greater than that of the measured concentrations (3 log$_{10}$ units, 1.05 to 986 ng/g lipid). However, the similar variance for the measured and modeled datasets in Fig. 2.2A (i.e. box size and whisker length), suggests that outliers drive the overall range difference. Particularly, this discrepancy is due to the lower bound of the model output, whereas the upper bound is in good agreement with the empirical data. In other words, for a relatively small number of individuals ($n = 338$) the model predicts concentrations that are much lower than measurements. A majority of these individuals ($n = 260$) reported no consumption of meat, fish or dairy products ($<1.0$ g lipid/d) on their 24-hour dietary recall surveys. Because the model assumes that only these three food categories contribute to a person’s dietary PCB intake, modeled body burdens of these individuals are unreasonably low ($<1$ ng/g lipid) due to exposure from inhalation and drinking water ingestion only.
It is likely that some of those 260 individuals actually eat meat or dairy products on a regular basis, but did not during the 24 hours to which the dietary recall survey applied. It is also likely that some individuals in NHANES ate a vegetarian diet. While the assumption that plant-based food contributes negligibly to PCB intake among those who also eat meat, fish and/or dairy is suitable, it is clearly unreasonable for vegetarians/vegans. Unlike more recent NHANES, there was no survey question that explicitly asked the participant if they consider themselves to be a vegetarian. The failure of the model to correctly predict the lower end of PCB exposure among NHANES participants could be addressed by not relying exclusively on 24-hour recall data for estimating dietary intake and by including foods such as grains, vegetables, and fruits in the model calculations.

2.3.3 Comparison of model predictions and measured data when stratified by sex, age, parity, BMI, and dietary lipid intake

Figure 2.2 also includes panels where measured and modeled PCB-153 concentrations are compared when the data are stratified by sex (Fig. 2.2B), age (Fig. 2.2C), number of children (Fig. 2.2D), BMI (Fig. 2.2E) and dietary lipid intake (Fig. 2.2F). Similar figures for PCB-118, -138, and -180 are shown in the Supporting Information, Figures 2.8, 2.9, 2.10). The model correctly reproduces associations between PCB exposure and certain variables (sex, age, number of children, BMI), but fails for others (dietary lipid intake).

Both the model estimates and measured data indicate that on average males have a slightly higher PCB-153 body burden than females (Fig. 2.2B), a sex-mediated effect supported by previous HBM studies. There are several factors contributing to higher predicted levels in males: first, they generally have a higher total dietary lipid intake (82 g lipid/d) than females (60 g lipid/d). Secondly, the model assumes that females have higher lipid contents than males for a given BMI, which could contribute to the lower levels observed in females (solvent dilution). Lastly, reproduction affords females two additional PCB loss processes: childbirth and breastfeeding.

When stratifying the data by age (Fig. 2.2C), the model reproduces the trend of rising PCB-153 body burdens with increasing age in the population cross-section. Such agreement is not surprising, because the agreement between modeled and measured trends with age served as a criterion during the optimization of E(t) and HLb. The model results for the non-optimized HLb and E(t) over-predict exposures for individuals older than 70 (see Supporting Information, Figure 2.6). Concentrations of
PCB-153 that increase monotonically with age in a cross sectional HBM study conducted during time periods of declining emissions have previously been explained by the older participants’ bodies retaining a “memory” of past exposures. [16, 20] Younger individuals, born after the peak in emissions, do not experience comparable PCB exposures.

In both the measured and modeled data, PCB-153 body burden increases with number of children (females only, Fig. 2.2D). This result may at first seem counterintuitive, since childbirth and nursing can significantly reduce PCB body burdens. [13] However, this may simply be because NHANES participants with more children are generally older. For example, the average birth year of mothers with 5 children is 1939, which resulted in higher PCB-153 body burdens because their lifetimes directly overlapped with the peak emission period. Similarly, mothers with 0 children include younger NHANES participants (i.e., <25 years of age), who have the lowest PCB-153 body burdens.

The relationship between PCB-153 body burden and BMI on the population level is subtle, but there is a trend of increasing model and measured PCB-153 concentration with increasing BMI, with the highest concentrations in those with BMIs in the 24.5-35 range (Fig. 2.2E). However, this BMI impact may simply reflect birth cohort, age, or time of sampling confounding, and may require further investigation. The literature is largely inconsistent in regards to associations between PCB body burden and BMI. [38–40]

Unlike other examined variables, the model identifies total dietary lipid intake as a significant contributor to PCB-153 concentrations, while the measured data indicate no differences in PCB-153 concentrations between the four lipid intake quartiles (Fig. 2.2F). The model suggests that PCB concentrations should increase with increasing lipid intake, a trend that will be discussed further in the next section describing individual model results.

### 2.3.4 Comparison of model predictions and measured data for individuals

Figure 2.3 directly compares modeled and measured concentrations for each individual NHANES participant. Model performance for the individual predictions is modestly successful. For example, 62% of all predicted data are within a factor of 3 of corresponding measured values, while 89% fall within one order of magnitude of measurements. Rank correlation between modeled and measured PCB-153 concentration was highly significant, with a Spearman $r_s = 0.44$. Considering the uncertainties inherent
Figure 2.2: Predicted (optimized scenario - blue; default scenario - green) and measured (red) log_{10} lipid-adjusted PCB-153 concentration (ng/g lipid) shown in box and whisker plots, organized by (A) all individuals, (B) sex, (C) age group, (D) number of children (females only), (E) BMI group, and (F) total dietary lipid intake. The ends of the whiskers represent the point closest to 1.5 times the interquartile range (IQR).
Figure 2.3: Predicted vs. measured log lipid-adjusted PCB-153 concentration (ng/g lipid). For each subplot, data is organized and coloured according to daily intakes (g lipid) of (A) total lipids, (B) beef lipids, (C) dairy lipids, and (D) fish lipids. The black dashed line represents the 1:1 line.

to the model calculation, such model performance is encouraging. However, the model fails to capture all sources of variability.

Discrepancies between modeled and measured PCB-153 levels are mainly due to the divergent impact of dietary lipid intake, as mentioned for population level predictions above (Fig. 2.2F). In each subplot of Figure 2.3, the data are colored according to the estimated individual intake of total lipids (panel A), beef lipids (B), dairy lipids (C), and fish lipids (D). Total dietary lipid intake (Fig. 2.3A) has a significant impact on the modeled concentrations ($R^2 = 0.44$), but virtually no impact on measured concentrations ($R^2 = 0.00$). This is readily observed in Figure 2.3A, where dietary intake quartile coloring stratifies along the predicted concentration axis (y axis), but not the measured concentration axis (x axis). The same is observed when only beef lipid intake (Fig. 2.3B, modeled data: $R^2 = 0.45$, measured $R^2 = 0.00$) and dairy lipid (Fig. 2.3C, modeled data: $R^2 = 0.11$, measured $R^2 = 0.00$) intake is considered. For fish lipid intake (Fig. 2.3D), there seems to be little association with either modeled ($R^2 = 0.02$) or measured concentrations ($R^2 = 0.03$). This is due to the fact that a majority of participants ($n = 3162$, or 52%) are assigned the default US average fish consumption (18.9 g ww/d before age adjustment), as they could not recall (“don’t know”) fish intake in their FFQ, or the data was missing.
2.4 Discussion

2.4.1 Comparison with previous studies predicting PCB exposure in individuals

This work complements two earlier studies that sought to mechanistically predict PCB exposure in individual humans. Nøst et al. [61] predict PCB concentrations in 554 Norwegian women who were either pregnant or postmenopausal; Binnington et al. [62] predicted PCB concentrations in 298 Arctic aboriginal mothers. Both studies used the PCB emissions by Breivik et al. [46] although without the shift of peak PCB emissions back 10 years that we employed.

Like the present study, Nøst et al. and Binnington et al. successfully reproduced mean population PCB exposures. For example, concentrations of PCB-153 predicted for Norwegian women were within one order of magnitude of measured values. [61] However, on an individual level the predictions were less effective, with the models again attributing a larger share of the exposure variability to dietary differences than was observed in the measured data. Our rank correlation coefficient between measured and modeled data ($r_s = 0.44$) is similar to those observed by Binnington et al. ($r_s > 0.40$ for each study group), and slightly lower than the value calculated by Nøst et al. ($r_s = 0.67$).

2.4.2 Reconciling differences between average and individual prediction success

Because the model is only moderately successful in predicting individuals’ PCB exposure using 24-hour dietary recall and FFQ data, it may at first be surprising that the population level predictions are so close to the average measured levels, considering that they are based on the average of those individual predictions. In parameterizing dietary intakes, our model approach requires a major assumption: the dietary recall from NHANES (24-hour period) is extrapolated to an individual’s entire lifetime, i.e., there are no changes in dietary composition with age or season. It is quite likely that an individual’s dietary intake within one particular 24-hour period is not entirely representative of their diet over an entire year, let alone a lifetime. On the other hand, the average of several thousand individuals’ dietary intakes from one particular 24-hour period may in fact be a reasonable estimate of the average of those individuals’ lifetime dietary intake. It is thus possible that personal dietary reports may poorly describe
actual individual intakes, but when sampled together in sufficiently large numbers may give an accurate representation of actual mean population consumption. In other words, a cancellation of errors in the individual NHANES estimated dietary intakes may be partly responsible for satisfactorily approximating dietary intake at the population level.

In addition, the unreliability of dietary recall data likely also contributed to the models ineffectiveness in accurately predicting individual exposures. In particular, the 24-hour recall and FFQ reports (which are used to estimate beef, dairy and fish consumption, respectively) are prone to recall bias, which leads to uncertain food consumption estimates. It has been reported previously that such methods tend to appreciably underestimate actual individual consumption rates. For example, NHANES energy intakes may be underreported by upwards of 800 kcal/day. Although we scaled up modeled dietary intakes to agree with the national US average diet, this does not address other known shortcomings of dietary intake data. For example, Freedman et al. observed that “across a diverse sample of Americans, subjective estimates of energy intake explained <10% of the variance of true intake”. Binnington et al. also identified the unreliability of dietary recall data as a key contributor to poor model performance for individuals. In particular, they noted that reported traditional food intake among Arctic populations had increased when compared to the previous decade, contradicting an expected decline in traditional food consumption. Furthermore, Shin et al. looked at estimating exposure to perfluorinated compounds, and also highlighted the need for better intake data to improve model estimates.

2.4.3 Evaluation of model predictions for environmental and food chain contamination

Considering the limitations of the dietary data, it is appropriate to also ask whether model-measurement agreement at the population level may be fortuitous. In order to explore this, we also compared the predicted PCB concentrations in air, sea water, fish, beef, and dairy lipids with measured values reported in the literature (Supporting Information, Section 2.5.7). Such a comparison is limited by the considerable variability of PCB concentrations in such samples and their potential to inadequately represent the average US food supply. Nevertheless, our modeled calculations are generally well within an order of magnitude of reported environment and food chain measurements. Often the agreement is much better, e.g. dairy concentrations (Supporting Information, Table 2.9). There is tendency for
concentrations in fish to be underpredicted (Supporting Information, Table 2.7) and those in beef/meat to be overpredicted (Supporting Information, Table 2.8).

Because the model-measurement agreement for the average levels in humans is better than model-measurement agreement for the food items, we suspect that the former is to some extent fortuitous, i.e., is a result of error cancellation. In particular, an overestimation of concentrations in meat could affect model results for humans, because NHANES participants on average consumed 47 times more meat lipids than fish lipids, and also because beef lipid intake correlates well with predicted PCB-153 exposure in our model calculations ($R^2 = 0.43$, data not shown). Overall, it is thus likely that discrepancies in model to measurement agreement for individuals are not only due to shortcomings in the reported dietary intake data (and its extrapolation to lifetime consumption), but also to deviations between predicted and observed PCB levels in various food items.

### 2.4.4 Other limitations of the model approach

Individuals with unique exposure scenarios, such as those who lived in close proximity to a PCB manufacturing plant, [69] are difficult to model with our approach. Additionally, individuals who consume locally produced livestock are difficult to describe because our model approach assumes that all individuals obtain their food from the same source, specifically the central US for beef and dairy, and the Pacific Ocean for fish. However, with geographical information and application of a regional-scale or nested’ fate and transport model, parameterized for particular locations/food origin scenarios, prediction of PCB levels for both groups of individuals could be achieved.

### 2.4.5 Conclusion

The low reliability of FFQs and 24-hour dietary recall data presently limits the feasibility of reconstructing individual exposure histories based on data typically collected in HBM studies. This implies that it may be difficult to improve exposure characterization in epidemiological studies of the health effect of contaminants through the use of such models, [70–72] unless the quality of dietary intake information is improved. It also implies that the presence or absence of statistical associations between measured PCB levels and the reported intake of certain dietary items may be more uncertain than previously recognized. On the other hand, the averages of dietary intake data appear to allow for reasonably good
predictions of both the mean and range of measured population PCB levels, especially if adjustment for
the known bias towards underestimation of energy intake is performed. [51,66] In particular, the ability
to reproduce statistical associations (or the lack thereof) between PCB concentrations and non-dietary
individual attributes such as age, sex, BMI or parity with the model approach is encouraging. It im-
plies that our model can mechanistically explain such associations and also make predictions of such
relationships. Lastly, the modelling approach described here can be adapted to national biomonitoring
campaigns of other countries, for example, the Canadian Health Measures Survey (CHMS).

2.5 Supporting Information

2.5.1 BETR-Global Input Parameters

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<thead>
<tr>
<th>Parameter</th>
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<td>Activation energy of degrading reactions (kJ/mol)</td>
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Table 2.1: Chemical properties used in BETR-Global.

a. Also used in ACC-Human
### 2.5.2 ACC-Human Model Input Parameters

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<td></td>
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</tr>
<tr>
<td>BMI 24.5 - 29.5 kg/m(^2)</td>
<td>1983</td>
<td></td>
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</tr>
<tr>
<td>BMI 29.5 - 35 kg/m(^2)</td>
<td>1091</td>
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</tr>
<tr>
<td>BMI &gt;35 kg/m(^2)</td>
<td>607</td>
<td></td>
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</tr>
<tr>
<td>0 childbirth(^b)</td>
<td>1503</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 childbirth(^b)</td>
<td>417</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2 childbirths(^b)</td>
<td>483</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 childbirths(^b)</td>
<td>342</td>
<td></td>
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<tr>
<td>4 childbirths(^b)</td>
<td>181</td>
<td></td>
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</tr>
<tr>
<td>5 childbirths(^b,c)</td>
<td>264</td>
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<td></td>
<td></td>
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<td>Common input parameters(^h)</td>
<td>Value</td>
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<td></td>
<td></td>
</tr>
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<td>Daily air intake (m(^3)/h)</td>
<td>15</td>
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<td></td>
<td></td>
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<tr>
<td>Daily water intake (L/d)</td>
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<td>PCB-153 biotransformation half-life (y)(^i)</td>
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<td>PCB-180 biotransformation half-life (y)(^i)</td>
<td>300</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2: Summary of selected input data to ACC-Human for NHANES participants

---

a. Birth year = sampling year - age at sampling. Birthday assumed to occur on December 31. The maximum human age in ACC-Human is 80. Model concentrations for NHANES participants older than 80 are “sampled” at a model age of 80.

b. Females only.

c. Maximum number of childbirths is truncated to 5.

d. A breastfeeding length of 6 months is assumed for individuals who reported breastfeeding any child.

e. Individuals who only had 1 child are excluded.

f. Maximum intake rate that occurs at age 25. Diet changes with age, but composition of diet is assumed constant over individual’s lifetime. Process to convert questionnaire response to daily dietary intake rates is discussed in detail below.

g. Individuals without a reported BMI value (n = 152) were assumed to have a BMI of 24.5-29 kg/m\(^2\).

h. Same for all individuals.

i. Fitted parameter.
2.5.3 BMI parameterization

22 unique BMI (kg/m$^2$) classifications were developed, in integers/whole numbers from 17 to 38. A unique growth curve describing changes in percent body fat (%BF) and body weight as a function of age and BMI were generated based on results published by Gallagher et al. [73] For males, a common body weight and lipid weight growth curve was assumed for all individuals aged 0-8. For ages 8-11, male individuals of different BMI classes were assumed to either gain or lose weight until they reach their designated BMI. From age 11 and onwards, these individuals live with their designated BMI for their entire lifetime (i.e. it is assumed that a person keeps the same BMI for their whole life). A plot of body weights and and lipid weights as a function of age and BMI for males is shown in Figure 2.4 below. Growth curves for females (not shown) were calculated in an identical manner as that of males, using results published by Gallagher et al. [73] except that female individuals diverge into their separate BMI classes beginning at age 12 (opposed to age 8 for males). All male model individuals have the same height (adult, 1.77 m) for a given age once they have diverged into their BMI class. The same is true for females (adult, 1.63 m).
Figure 2.4: Human male growth curves - total body mass (red) and lipid mass (blue) as a function of age for each of the 22 BMIs.

2.5.4 Conversion of dietary questionnaire information to model input

The dietary interview - individual foods (DRXIFF file) was used to construct daily intake rates of animal lipids and dairy lipids. The dietary interview catalogues all food the individual eats over a 24-hour period, including total food weight. Importantly, total fat is included for each food item. For meat, the total fat is summed from any and all food items that mention beef, turkey, chicken, pork, veal, or
lamb for each individual. For dairy, the keywords are milk, dairy, ice cream, cheese, yogurt, and butter. The determined dairy lipid and animal lipid values become model input for daily intake rates (g lipid / d) of these food groups.

For fish, a different approach was taken. The dietary questionnaire on total nutrient intakes (DRX-TOT file) included a section on fish consumption frequency. These questions asked about consumption of various fish species, and if so, how many times in the past 30 days such fish was eaten. A daily intake rate of fish (g wet weight / d) was estimated by totalling the number of fish a person ate, followed by multiplying this total by an assumed serving size of 85 g (3 oz) and dividing by 30 d.

Additionally, a national average for American consumption of each food group (fish, dairy lipid, animal lipid) was estimated using the United States Department of Agriculture’s (USDA) Agricultural Fact Book - Chapter 2 - Profiling Food Consumption in America. [74] These estimates are shown in Table 2.3 below. Daily rates of lipid intake were estimated using an assumption for fat content (obtained from relevant food items in USDA National Nutrient Database) of each food item.

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount per year (lbs)</th>
<th>% Fat</th>
<th>Daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>13.6</td>
<td>10%</td>
<td>1.69 g lipid / d</td>
</tr>
<tr>
<td>Veal + lamb</td>
<td>1.4</td>
<td>15%</td>
<td>0.26 g lipid / d</td>
</tr>
<tr>
<td>Chicken</td>
<td>52.9</td>
<td>10%</td>
<td>6.57 g lipid / d</td>
</tr>
<tr>
<td>Beef</td>
<td>64.4</td>
<td>15%</td>
<td>12.0 g lipid / d</td>
</tr>
<tr>
<td>Pork</td>
<td>47.7</td>
<td>10%</td>
<td>5.92 g lipid / d</td>
</tr>
<tr>
<td>Total meat</td>
<td>180</td>
<td>N/A</td>
<td>26.4 g lipid / d</td>
</tr>
<tr>
<td>Total dairy</td>
<td>593</td>
<td>4.4%</td>
<td>32.4 g lipid / d</td>
</tr>
<tr>
<td>Total fish and shellfish</td>
<td>15.2</td>
<td>N/A</td>
<td>18.9 g wet weight / d</td>
</tr>
</tbody>
</table>

Table 2.3: National estimate of average daily intake of relevant food items.

A scaling factor was applied to the individual daily intake rates determined (total meat, total dairy, total fish) above. This scaling factor was determined by dividing the national intake estimates from Table 2.3 by the average of all individual daily intake estimates for each NHANES (e.g., 1999-2000, 2001-2002, 2003-2004). For fish consumption, this factor was 2.1 (NHANES 1999-2000), 2.0 (NHANES 2001-2002), or 1.9 (NHANES 2003-2004). For total meat consumption, this factor was 1.6 (NHANES 1999-2000), 1.6 (NHANES 2001-2002), or 1.5 (NHANES 2003-2004). Lastly, for total dairy consumption, this factor was 1.5 (NHANES 1999-2000), 1.4 (NHANES 2001-2002), or 1.4 (NHANES 2003-2004).
The model specifies dietary intake at age 25 as an input parameter. The default dietary intake rate is a function of age. [15] For females:

\[ I_{\text{default}}(age) \text{ (g dry weight/h)} = 0.0000007044 \times age^5 - 0.00020058 \times age^4 + 0.022579 \times age^3 \]
\[ - 1.346 \times age^2 + 39.22 \times age + 46.199)/24 \]

And for males: [15]

\[ I_{\text{default}}(age) \text{ (gdryweight/h)} = (100 + 510 \times (1 - \exp((-(age/12)^{1.4})))) - 0.1 \times ((age - 20)^2 - 5 \times age))/24 \]

where age is the age of human individual in years. The model requires the intake rate at 25 years of age as input [15]. Each individual’s dietary intake rates at their current age, derived from the questionnaire responses, \( I_{\text{individual}}(age) \), was adjusted to age 25 using:

\[ I_{\text{individual}}(25) = I_{\text{default}}(25) \times I_{\text{individual}}(Age)/I_{\text{default}}(Age) \]

Where and \( I_{\text{default}}(25) \) and \( I_{\text{individual}}(25) \) are calculated using either of the two previous equations.

### 2.5.5 Optimization of emissions timing and human biotransformation half-life

Figure 2.5 below illustrates the general concept of an “emissions shift”. The unmodified emission scenario from Breivik et al. [46] peaks around 1970. Two additional emission scenarios were devised: 5 years shift (1965) and 10 years shift (1960). The environmental fate for PCBs -118, -138, -153, and -180 for each of these scenarios was calculated using BETR-Global. This was then combined with a general ACC-human simulation, for both males and females, assuming US national estimates of beef, dairy, and fish intake (Table 2.3, derived above). Human biotransformation half-life was varied from 1 year to 300 years, with values every 1 year from 1 to 30, and every 10 years thereafter. Three cross-sectional body burden age trends (CBATs) were calculated for years representing NHANES events: 2004 (NHANES 2003-2004), 2002 (NHANES 2001-2002), and 2000 (NHANES 1999-2000). The ACC-Human-generated CBATs were compared with a median CBAT obtained from the NHANES biomonitoring data. The sum of squared residuals (SSR) was summed from the three comparisons (NHANES 1999-2000, 2001-2002,
for each combination of biotransformation half-life and emissions shift. The combination of biotransformation half-life and emissions shift that yielded the smallest SSR was selected as the optimal value, with the condition that the optimal values all come from the same emissions shift (i.e., there would be no selection of a 0 year emission shift and 10 year half-life for PCB-138 while PCB-118 has a 10 year emission shift and 10 year half-life). For PCB-118, -138, -153, and -180, a 10 year emission shift resulted in the lowest SSR. We report optimized human biotransformation half-lives of 8, 25, 35, and 300 years for PCB-118, -138, -153, and -180, respectively. Figure 2.6 (males) illustrates the model-measurement agreement improvement (for the average person) as a result of constraining these input parameters. All model predictions (for PCB-118, -138, -153, and -180) used these optimized values. We did not consider moving the peak in emissions forward in time because this would exacerbate the over-prediction of PCB levels in younger individuals rather than diminish them. We have also included the model results for the default/original scenario in Figure 2.7 below.

![Illustrative example of an “emissions shift”](image.png)

**Figure 2.5:** Illustrative example of an “emissions shift”. Note that the emission profile is exactly the same, only shifted ten years to the left (into the past).
Figure 2.6: Comparison of male CBATs for each NHANES (1999-2000, 2001-2002, 2003-2004) for unadjusted emission scenario and default biotransformation half-life (blue), 10-year adjusted emissions shift and adjusted biotransformation half-life (orange), and measured CBAT from NHANES (red). The adjusted CBAT (orange) represents the best human biotransformation half-life that closely reproduces the CBAT from NHANES. The default half-lives used for PCB congeners 118, 138, 153, and 180 were 3, 8, 15, and 231 years, respectively.
Figure 2.7: Predicted (default/original scenario results; green) and measured (red) log10 lipid-adjusted PCB-153 concentration (ng/g lipid) shown in box and whisker plots, organized by (A) all individuals, (B) sex, (C) age group, (D) number of children (females only), (E) BMI group, and (F) total dietary lipid intake. The ends of the whiskers represent the point closest to 1.5 times the interquartile range (IQR).
2.5.6 Additional model results for PCB-118, -138, and -180

<table>
<thead>
<tr>
<th>Statistic</th>
<th>PCB-118 (n=6107)</th>
<th>PCB-138 (n=6112)</th>
<th>PCB-153 (n=6128)</th>
<th>PCB-180 (n=6107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>12.1</td>
<td>10.4</td>
<td>27.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Median</td>
<td>5.4</td>
<td>6.7</td>
<td>15.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Min</td>
<td>0.7</td>
<td>0.001</td>
<td>1.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Max</td>
<td>361</td>
<td>143</td>
<td>773</td>
<td>398</td>
</tr>
<tr>
<td>R²</td>
<td>0.01</td>
<td>0.08</td>
<td>0.11</td>
<td>0.16</td>
</tr>
<tr>
<td>R², total lipid</td>
<td>0.00</td>
<td>0.60</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>R², fish</td>
<td>0.03</td>
<td>0.01</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>R², dairy</td>
<td>0.00</td>
<td>0.15</td>
<td>0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>R², beef</td>
<td>0.00</td>
<td>0.62</td>
<td>0.00</td>
<td>0.48</td>
</tr>
<tr>
<td>R², age</td>
<td>0.23</td>
<td>0.04</td>
<td>0.30</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Table 2.4: Mean, medians, and other statistical measures of the model comparison. Statistics for PCB-153 is provided for comparison. R² values are provided for linear regressions between PCB concentrations (model, measured) and certain model input parameters (e.g., model PCB concentrations vs. total lipid intake).

The following figures show results for PCB-118 (Figure 2.8), -138 (Figure 2.9), and -180 (Figure 2.10), respectively in box and whisker plots. Similar to the model results for PCB-153, the model results for these other congeners reproduce the average measured levels. They also reproduce trends with age, sex, BMI (except PCB-118), and parity (number of children), and, identical to the results for PCB-153, the model suggests that PCB concentrations should increase with increasing lipid intake, while the measured data demonstrates no change in PCB concentrations with lipid intake.

The following figures are similar to Figure 2.3 (scatterplots) in the main text, but for congeners 118 (Figure 2.11), 138 (Figure 2.12), and 180 (Figure 2.13).
Figure 2.8: Predicted (blue) and measured (red) log\(_{10}\) lipid-adjusted PCB-118 concentration (ng/g lipid) shown in box and whisker plots, organized by (A) all individuals, (B) sex, (C) age group, (D) number of children (females only), (E) BMI class, and (F) total dietary lipid intake.
Figure 2.9: Predicted (blue) and measured (red) log_{10} lipid-adjusted PCB-138 concentration (ng/g lipid) shown in box and whisker plots, organized by (A) all individuals, (B) sex, (C) age group, (D) number of children (females only), (E) BMI class, and (F) total dietary lipid intake.
Figure 2.10: Predicted (blue) and measured (red) $\log_{10}$ lipid-adjusted PCB-180 concentration (ng/g lipid) shown in box and whisker plots, organized by (A) all individuals, (B) sex, (C) age group, (D) number of children (females only), (E) BMI class, and (F) total dietary lipid intake.
Chapter 2. Modelling PCB-153 Exposure in Individual Humans

Figure 2.11: Predicted vs. measured log lipid-adjusted PCB-118 concentration (ng/g lipid). For each subplot, data is organized and coloured according to daily intakes (g lipid) of (A) total lipids, (B) beef lipids, (C) dairy lipids, and (D) fish lipids. The black dashed line represents the 1:1 line.

Figure 2.12: Predicted vs. measured log lipid-adjusted PCB-138 concentration (ng/g lipid). For each subplot, data is organized and coloured according to daily intakes (g lipid) of (A) total lipids, (B) beef lipids, (C) dairy lipids, and (D) fish lipids. The black dashed line represents the 1:1 line.
Figure 2.13: Predicted vs. measured log lipid-adjusted PCB-180 concentration (ng/g lipid). For each subplot, data is organized and coloured according to daily intakes (g lipid) of (A) total lipids, (B) beef lipids, (C) dairy lipids, and (D) fish lipids. The black dashed line represents the 1:1 line.

2.5.7 Model evaluation for Environmental and Dietary Concentrations

PCB concentrations measured in air over the United States agree well with model predictions, i.e., within one order of magnitude (Table 2.5). In particular, model estimates for PCB-118 concentrations in air were commonly within a factor of 2 of the measured values. Measured PCB-153 concentrations in air were reported as the sum of congeners 105, 132, and 153, which may be partially responsible for the model’s underestimation of the air concentration of PCB-153. A model underestimation was also observed for congeners 138 and 180.
Table 2.5: Comparison between model estimates for PCB concentrations in air with measured levels. All values are in pg/m\(^3\).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Location</th>
<th>Note</th>
<th>PCB-118</th>
<th>PCB-138</th>
<th>PCB-153</th>
<th>PCB-180</th>
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<tbody>
<tr>
<td>Hornbuckle et al. [75]</td>
<td>1993</td>
<td>University of Wisconsin - Green Bay</td>
<td></td>
<td>2.32</td>
<td>n/a</td>
<td>8.95(^a)</td>
<td>2.49</td>
</tr>
<tr>
<td>Model</td>
<td>1993</td>
<td>Box 78(^b)</td>
<td></td>
<td>1.43</td>
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<td></td>
<td>Box 79(^c)</td>
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<td>2.67</td>
<td>2.48</td>
<td>0.92</td>
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<tr>
<td>Simcik et al. [76]</td>
<td>1995</td>
<td>Lake Michigan</td>
<td>Winds SW Winds N</td>
<td>10.1</td>
<td>13.5</td>
<td>24.4(^a)</td>
<td>8.6</td>
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</tr>
<tr>
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<td>Box 78(^b)</td>
<td></td>
<td>0.83</td>
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<tr>
<td>Gouin et al. [78]</td>
<td>2002</td>
<td>Southern Ontario</td>
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<td>Box 78(^b)</td>
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<td>0.78</td>
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<td>Box 79(^f)</td>
<td></td>
<td>1.49</td>
<td></td>
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</tr>
</tbody>
</table>

Model PCB concentrations in Pacific Ocean seawater (Table 2.6) were about one order of magnitude lower than the measured levels. However, model predictions for other oceanic regions (e.g., Atlantic...
ocean, US east coast, and coastal waters of western Europe and western Africa) were much more rea-
sonable, generally within a factor of 2.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Location</th>
<th>PCB-118</th>
<th>PCB-138</th>
<th>PCB-153</th>
<th>PCB-180</th>
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<td>Zhang &amp; Lohmann [79]</td>
<td>2006-2007</td>
<td>Northern Pacific Ocean</td>
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<td>0.9</td>
<td>1.7</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Model</td>
<td>2006</td>
<td>0.08</td>
<td>0.06</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2007</td>
<td>0.08</td>
<td>0.05</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Lohmann et al. [80]</td>
<td>2009</td>
<td>40.5N, 71.2W</td>
<td>0.37</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36.0N, 70.0W</td>
<td>0.13</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Model</td>
<td>2009</td>
<td>Box 79(^a)</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Box 80(^b)</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gioia et al. [81]</td>
<td>2005</td>
<td>West Africa coast, west Europe seawater</td>
<td>0.04</td>
<td>0.1</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Model</td>
<td>2005</td>
<td>Box 60(^d)</td>
<td>0.08</td>
<td>0.07</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Box 80(^d)</td>
<td>0.16</td>
<td>0.10</td>
<td>0.13</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Box 84(^d)</td>
<td>0.15</td>
<td>0.15</td>
<td>0.22</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Box 107(^d)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.07</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 2.6: Comparison between model estimates for PCB concentrations in seawater with measured levels. All values are in ng/m\(^3\).

a. Pacific ocean adjacent to California coast
b. Seawater directly adjacent to US east coast
c. Includes locations from Lohmann et al.
d. Includes locations that were sampled in Gioia et al.
e. Seawater in Atlantic ocean, near US east coast (for comparison)
## Chapter 2. Modelling PCB-153 Exposure in Individual Humans

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Location</th>
<th>Fish</th>
<th>PCB-118</th>
<th>PCB-138</th>
<th>PCB-153</th>
<th>PCB-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Froescheis et al. [82]</td>
<td>1995</td>
<td>Monterey Bay</td>
<td>Petrale sole</td>
<td>22</td>
<td>52</td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>Canyon, California</td>
<td>Rockfish</td>
<td>37</td>
<td>84</td>
<td>75</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>(Northeast Pacific)</td>
<td>Dover sole</td>
<td>50</td>
<td>153</td>
<td>163</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>California</td>
<td>Thornyhead</td>
<td>43</td>
<td>176</td>
<td>234</td>
<td>390</td>
</tr>
<tr>
<td>Schecter et al. [28]</td>
<td>1995</td>
<td>Purchased in U.S. Supermarkets</td>
<td>Ocean fish(^{a})</td>
<td>22.7</td>
<td>30.8</td>
<td>27.9</td>
<td>12.0</td>
</tr>
<tr>
<td>Model age 0-5 y</td>
<td>1994</td>
<td>Box 76</td>
<td>Cod</td>
<td>5</td>
<td>4.69</td>
<td>4.45</td>
<td>5.10</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td></td>
<td>Herring</td>
<td>5</td>
<td>3.15</td>
<td>3.15</td>
<td>3.47</td>
</tr>
<tr>
<td>Model age 0-10 y</td>
<td>1994</td>
<td>Box 76</td>
<td>Cod</td>
<td>5</td>
<td>4.16</td>
<td>3.93</td>
<td>4.51</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td></td>
<td>Herring</td>
<td>5</td>
<td>2.84</td>
<td>2.81</td>
<td>3.09</td>
</tr>
</tbody>
</table>

Table 2.7: Comparison between model estimates for fish PCB concentrations and measured levels. All values in ng/g lipid.

\(^{a}\) Fresh salmon steak, king salmon steak, true cod filets, ocean perch filets, sea bass, halibut, true cod filets, fresh scrod/cod, fresh/frozen cod filets, tiger prawns

In general, we are overestimating concentrations in meat (Table 2.8), whereas levels in dairy items are predicted reasonably accurately (Table 2.9). More specifically, meat is overestimated by at least a factor of 1.7 (except in cases of hot dog / balogna for PCB-180); in some instances our model estimates are 9.4 to 20.8 times higher.
Table 2.8: Comparison between model estimates for animal lipid PCB concentrations and measured levels. All values in pg/g lipid. PCB concentrations in lipid from Schecter et al. were estimated using the reported lipid content (a-d).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Location</th>
<th>Animal/meat</th>
<th>n</th>
<th>PCB-118</th>
<th>PCB-138</th>
<th>PCB-153</th>
<th>PCB-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schecter et al. [28]</td>
<td>1995</td>
<td>Supermarkets across USA</td>
<td>Beef(^a) n/a</td>
<td>717.6</td>
<td>ND</td>
<td>633.6</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chicken(^b) n/a</td>
<td>ND</td>
<td>754.7</td>
<td>2094.3</td>
<td>4339.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pork(^c) n/a</td>
<td>1065.2</td>
<td>782.6</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hot dog/bologna(^d) n/a</td>
<td>3706.3</td>
<td>3010.5</td>
<td>1958.0</td>
<td>489.5</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>1995</td>
<td>Box 78</td>
<td>Beef 1</td>
<td>1369</td>
<td>1115</td>
<td>1372</td>
<td>434</td>
<td></td>
</tr>
<tr>
<td>Kim et al. [83]</td>
<td>2001</td>
<td>United States, domestic and imported products</td>
<td>Beef</td>
<td>53</td>
<td>58.14</td>
<td>106.35</td>
<td>73.4</td>
<td>45.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chicken 30</td>
<td>52.31</td>
<td>92.17</td>
<td>28.3</td>
<td>18.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pork 66</td>
<td>27.96</td>
<td>108.72</td>
<td>65.08</td>
<td>32.9</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>2001</td>
<td>Box 78</td>
<td>Beef 1</td>
<td>886</td>
<td>744</td>
<td>925</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>Winters et al. [84]</td>
<td>1993</td>
<td>United States</td>
<td>Cattle (back fat)</td>
<td>63</td>
<td>448.6</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Model</td>
<td>1993</td>
<td>Box 78</td>
<td>Beef 1</td>
<td>1665</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.9: Comparison between model estimates for dairy PCB concentrations and measured levels. All values in pg/g lipid. PCB concentrations in dairy from Schecter et al. were estimated using the reported lipid content (a, b).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Location</th>
<th>Item</th>
<th>n</th>
<th>PCB-118</th>
<th>PCB-138</th>
<th>PCB-153</th>
<th>PCB-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schecter et al. [28]</td>
<td>1995</td>
<td>United States</td>
<td>Cheese(^a) n/a</td>
<td>1119</td>
<td>674</td>
<td>748</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supermarkets</td>
<td>Butter(^b) n/a</td>
<td>1038</td>
<td>882</td>
<td>774</td>
<td>276</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>1995</td>
<td>Box (USA)</td>
<td>Milk 1</td>
<td>399</td>
<td>308</td>
<td>396</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Santillo et al. [86]</td>
<td>1998-1999</td>
<td>USA - East Coast</td>
<td>Butter 1</td>
<td>420</td>
<td>390</td>
<td>440</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA - Great Lakes</td>
<td>Butter 1</td>
<td>210</td>
<td>260</td>
<td>290</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>1998</td>
<td>Box (USA)</td>
<td>Milk 1</td>
<td>321</td>
<td>253</td>
<td>327</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>Box (USA)</td>
<td>Milk 1</td>
<td>298</td>
<td>236</td>
<td>306</td>
<td>92.6</td>
<td></td>
</tr>
</tbody>
</table>

a. Lipid content = 13.1%  
b. Lipid content = 5.3%  
c. Lipid content = 9.2%  
d. Lipid content = 28.6%
2.5.8 Calculation of intrinsic half-lives

Intrinsic elimination half-lives for each PCB congener (4) was calculated using data from various model calculations - e.g., males and females (2), of each BMI class (17 to 38 kg/m$^2$, 22 total), cohorts 1950 to 1980 (4), eating the average diet (Table 2.2), with mothers having one child at the average age of 22 years (Table 2.2). The intrinsic half-life was calculated over the time period 1990-2030 by removing all sources of exposure (dietary, water, and air) over this time period and fitting a first-order exponential decay function ($\log_e$ PCB concentration vs time, data not shown; $R^2$ often $>$0.98). The resulting half-lives are shown below, Figure 2.14, with the data organized according to PCB congener, sex, cohort, and BMI.

These results indicate that intrinsic half-life increases with BMI for all congeners, and that for a given BMI, older age is associated with longer intrinsic elimination half-life. Generally, females have a longer intrinsic half-life for a given cohort, BMI, and congener. For PCB-118, the half-life can range from 2 y to 7 y; PCB-138 from 2 y to 18 y; PCB-153 from 3 y to 24 y; and PCB-180 from 3 y to 50 y. For females, the low elimination half-life for the 1980 cohort is due to childbirth being a significant elimination process during this time period (child birth at the age of 22, or the year 2002).
Figure 2.14: Intrinsic elimination half-lives over the time period 1990-2030 as a function of BMI for each PCB congener (rows), organised by sex (columns), and cohort (1950-1980; different coloured lines).
Chapter 3

Unravelling the relationship between body mass index and polychlorinated biphenyl concentrations using a mechanistic model


Contributions: The model(s) used for this research project was previously developed and published by G. Czub and M. MacLeod. Modelling assistance was provided to S. Wood by J. Armitage. S. Wood ran the model and interpreted model results under the guidance of F. Wania. S. Wood and F. Xu wrote the manuscript under the guidance of F. Wania.
3.1 Introduction

Polychlorinated biphenyls (PCBs) are a group of well-recognized persistent organic pollutants (POPs) that have the potential for neurological, developmental, and reproductive toxicity [87–90] as well as high bioaccumulation [15] and long-range transport potential. [91] Although the production of PCBs was prohibited by the United States Congress in 1979, the persistence of these chemicals, as well as continuing low-level emissions from primary sources (e.g., buildings and electrical equipment built in earlier decades) and environmental reservoirs (e.g., soil), make it impossible to completely eliminate human exposure to these pollutants. The presence of PCBs in the human body is still a health concern, and the potential health repercussions from PCB exposure are expected to persist for several decades. [13,92]

Human biomonitoring (HBM) data are an important component of epidemiological studies aimed at understanding long-term health effects of contaminants. In this context it is important to establish that any observed associations between contaminant levels and adverse health outcomes are not a result of toxicokinetics. [93] In particular, toxicokinetics may confound efforts to establish a possible obesogenic effects of POPs based on HBM data; [94] because of their hydrophobicity and resultant preference to be stored in lipids, the amount of body fat in an individual is expected to profoundly affect the toxicokinetics of POPs. In other words, we would expect that obesity itself influences POP concentrations.

While many studies have reported that lipid-normalized body burdens (i.e., the total mass of contaminant in the organism divided by the lipid mass, expressed as ng/g lipid) for PCBs and other POPs are negatively associated with body adiposity due to the dilution effect, [50,95,96] overall, the relationship between POP body burden and body mass index (BMI; a surrogate for body adiposity with the units kg/m²) are inconsistent, showing negative, positive or no associations. [38–40] To explain the apparent contradiction between cross-sectional body burden versus BMI trends (CBBTs) from different studies, Wolff et al. [50] hypothesized that these divergent relationships are a result of variable toxicokinetics in lean and obese individuals during times of increasing and decreasing exposure: when exposure rises, POP concentrations tend to be lower in obese people than in lean individuals due to a dilution effect, while during periods of declining exposure POP concentrations in obese individuals will eventually overtake those of lean people, because elimination from the human body is slower for obese individuals. Thus, a “cross-over” where the body burden of obese individuals overtakes those of lean people was predicted for dichlorodiphenyltrichloroethane (DDT) around 1982. [50] For PCBs, however, this “cross-over” does not seem to have occurred yet, as various studies reported a negative correlation between lipid-normalized
body burden and BMI. [40, 97] To our knowledge, no attempt has been made so far to use mechanistic human exposure models to further evaluate Wolff et al.’s hypothesis.

An important demographic phenomenon that could potentially influence the population-level PCB body burdens is the obesity epidemic, which has led to a significant increase in the prevalence of obesity (BMI ≥ 30 kg/m²) in the United States from 12.8% in 1960-62 to 35.5% in 2009-2010. [98, 99] Whereas the concentrations of PCBs in humans have decreased over the past few decades, [45] it is yet unclear to what degree the onset of the obesity epidemic has influenced the temporal trend in population level PCB body burdens in the U.S. Adding to the complexity of the interplay between population body burden trends and increasing BMI is the effect of population aging (e.g., increased longevity combined with the baby boom'). Because older Americans tend to have higher concentrations of PCBs, population averages could be influenced as the prevalence of such individuals in the general population (or survey cohort) increases.

The main objectives of this study are to (i) demonstrate how mechanistic models, such as the bioaccumulation model ACC-Human, [15] can be effective tools for evaluating the relative importance of factors which potentially influence body burden (e.g., BMI, age, emission history); (ii) test the plausibility of the hypothesis by Wolff et al. [50] using ACC-Human and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153), a PCB congener frequently detected in humans, and (iii) to investigate the effect of the obesity epidemic and population aging on population PCB-153 body burden.

3.2 Methods

The simulation data upon which this study is based are from a mechanistic prediction of the exposure of individual NHANES participants to PCB-153, which has been presented earlier, in Chapter 2. Figure 3.1 provides an overview of the simulation procedure.

3.2.1 Model Description

All simulations were performed using a combination of the BETR-Global model [25] - a mechanistic, global scale, environmental fate and transport model - and the human food chain bioaccumulation model.
ACC-Human. [15] BETR-Global simulates the distribution of time-variant emissions of an organic chemical between different environmental compartments (e.g., the atmospheric, soil, aqueous, and sediment compartments), while the ACC-Human model takes these environmental concentrations and simulates bioaccumulation in the food web and in humans. Some basic input information required by BETR-Global includes the contaminant’s octanol-air and octanol-water equilibrium partition coefficients (log $K_{OA}$ and log $K_{OW}$, respectively), environmental degradation half-lives, and historical time-variant emissions. ACC-Human requires information on time-variant environmental contamination (calculated by BETR-Global), and human specific input parameters, including year of birth, sex, body mass index, dietary intake of lipids (fish, beef, and dairy), and, in the case of mothers, reproductive behaviour (parity, mother’s age at childbirth, and nursing duration). The model was run from 1930 (the beginning of PCB production in the United States) until 2100. For a complete description of the model approach, refer to Chapter 2 and references therein. A summary of model input parameters can be found in Tables 2.1 and 2.2.

### 3.2.2 Growth curve specifications

Because of the importance of the BMI parameterization in the ACC-Human model for the current study, a detailed description is provided here. Definitions of obesity and body mass index classifications were adopted from Flegal et al. [98] and the World Health Organization. [100] Under the assumption that BMI can be used to estimate body adiposity, five different BMI classes were defined: BMI $< 19.5$ kg/m$^2$ (underweight), BMI = 19.5-24.4 kg/m$^2$ (normal), BMI = 24.5-29.4 kg/m$^2$ (pre-obese), BMI = 29.5-34.4 kg/m$^2$ (Class I Obesity), BMI $\geq$ 34.5 kg/m$^2$ (Class II and Class III Obesity). For this study, varying BMI values of 17 to 38 kg/m$^2$ (inclusive), in increments of 1, were chosen to represent the five BMI classes during simulations. For example, BMI values of 17, 18, and 19 kg/m$^2$ represent the underweight ($< 19.5$ kg/m$^2$) BMI class. Additionally, an individual’s reported BMI in the NHANES questionnaire was rounded to the nearest whole number. Individuals with a BMI less than 17 or greater than 38 were assumed to have a BMI of 17 or 38, respectively, in the model calculations. For each BMI, growth curves describing changes in percent body lipid (%BF) and body weight as a function of age and BMI were developed based on results published by Gallagher et al. [73] (Example curve for BMI = 27 kg/m$^2$ male, Figure 3.1C, for all male growth curves, see Figure 2.4; for Females, see Figure 3.6). For males, common body weight growth curve was assumed for children aged 0-8. From age 8-11, male children of different BMI classes were assumed to linearly gain (or lose) weight until they reach their designated BMI class.
Figure 3.1: Schematic overview of how the BETR-Global and ACC-Human models estimate CBBTs for PCB-153: historical atmospheric emissions (A; from Breivik et al. 2010 [12]) are used to calculate time-variant PCB-153 concentrations in exposure-relevant environmental media (B) using the BETR-Global environmental fate model. Information on participants from NHANES 1999-2004 (year of birth, age at sampling, BMI, sex, reproductive behaviour, and dietary intake), and unique growth curves based on BMI (C; BMI = 27 kg/m$^2$ shown) are used to calculate longitudinal PCB-153 body burden for individuals of different BMI classes (D; males born in 1965-1974 shown) using the ACC-Human bioaccumulation model. Lastly, CBBTs for the years 1990, 2005, and 2040 (E) are derived by “sampling” this cohort.
From age 11 and onwards, these young adult males lived and aged within their assigned BMI level. For females, a common growth curve was used for ages 0-11. For age 11-15, female children of different BMI were assumed to linearly gain (or lose) weight until they reached their designated BMI. From age 15 and onwards, these young adult females lived and aged within their assigned BMI.

### 3.2.3 Model calculations and generating cross-sectional trends

We calculated longitudinal body burden age trends (LBATs, Figure 3.1D) of PCB-153 in the human body for NHANES 1999-2004 [4] participants born during the time period from 1915 to 1992 (n = 6128, eight distinct birth cohorts, e.g., 1920 cohort would represent those born 1915 to 1924, 1930 cohort for births 1925 to 1934, and so on). The human sub-model within ACC-Human was run once for each study participant using questionnaire information (from NHANES) on their year of birth, sex, BMI, dietary intake of fish, beef lipids, and dairy lipids, and for mothers, number of childbirths, mother’s age at childbirth, and nursing duration. More importantly, each study participant was assigned to one of 22 unique growth curves based on their BMI reported in the NHANES questionnaire. Each of the 6128 model generated LBATs was sorted according to their birth cohort (8), BMI class (5), and sex (2), and averaged to generate 80 unique LBATs (Males from the 1980 cohort shown in Figure 3.1D). We additionally added two hypothetical birth cohorts: individuals born in the years 1900 and 1910, for each BMI class (5), and both sexes (20 additional LBATs), bringing the total number of modeled birth cohorts to 10. These hypothetical individuals allow us to simulate individuals born before the oldest NHANES individuals (i.e., earlier than 1915). Lastly, CBBTs were simulated by “sampling” different birth cohorts in several historical and future sampling years (Figure 3.1E). Note that an individual’s dietary intake of animal lipids parameterized according to the NHANES dietary recall and food frequency questionnaire was not correlated with their BMI (Spearman correlation $r = -0.021$; see Supporting Information, Table 3.1, for averages of dietary intake among different BMI classes).

### 3.2.4 Investigating the influence of biotransformation half-life and partitioning properties

Two factors that are hypothesized to influence the shape of CBBTs is human biotransformation half-life of a contaminant and its equilibrium partitioning properties. To better understand their influence,
we simulated exposure for three additional PCB congeners: PCB-118 (8 year biotransformation half-life), PCB-138 (25 year biotransformation half-life) and PCB-180 (300 year biotransformation half-life). Additional physicochemical properties for these other congeners can be found in Chapter 2.5.1, Table 2.1. All simulations were performed using the same human model input for the 6128 NHANES participants, as described above.

3.2.5 Population level estimations

Information on age group-specific and gender-specific BMI distributions for the American population, [98–100] as well as historical data on the American population age distribution, [101] were used to convert the simulated time trends of PCB-153 body burden in different birth cohorts and different BMI classes into a population average body burden for U.S. males and females aged 20-80 from the years 1980 to 2010. The influence of demographic changes - such as population aging and the obesity epidemic - on population average body burdens were also evaluated by performing the same calculations multiple times, with the population age distribution, the age and gender specific BMI distribution, or both, fixed at the 1980 level. Information on these age and BMI distributions can be found in the Chapter 3.4, Tables 3.2 to 3.5.

3.2.6 Model Evaluation

To assess the performance of the modeling approach, we calculated the model bias (MB) and absolute model bias (AMB) using the equations shown below. [102]

\[
MB = \frac{1}{n} \sum_{i=1}^{n} \log_{10} \left( \frac{C_{\text{model},i}}{C_{\text{measured},i}} \right) \quad (3.1)
\]

\[
AMB = \frac{1}{n} \sum_{i=1}^{n} \log_{10} \left| \frac{C_{\text{model},i}}{C_{\text{measured},i}} \right| \quad (3.2)
\]

The average factor of agreement between model predictions and measurements is then \(10^{MB}\) and \(10^{AMB}\). The AMB metric accounts for error cancellation and therefore better reflects the accuracy of the model predictions.
3.3 Results and Discussion

3.3.1 Comparison with NHANES Measured Data

The previous chapter (2) evaluated the model calculations on which the current analysis is based and found that the model successfully reproduced trends of PCB concentrations with variables such as age, sex, and parity. In particular, the model reproduced the CBBT at the whole population level (Figure 2.1A in Chapter 2). In order to further evaluate the accuracy of our model, Figure 3.2 compares model estimates for each individual cohort with lipid-adjusted PCB-153 concentrations (ng/g lipid) reported in NHANES. Agreement between simulated values and empirical data is within a factor of three on average for adult males (model bias - equation 1; MB = -0.11, absolute model bias - equation 2; AMB = 0.46), and for the entire dataset (MB = -0.22, AMB = 0.48).

Notably, the general trend of the CBBTs is closely captured by most of the simulations (e.g., males born in 1980, and 1990, Figure 2E and F), suggesting that the mechanistic model we used possessed predictive power. The large variance of both measured and modelled NHANES data is the result of other variables such as the person’s exposure history, dietary habits and life history. Similar results for female participants from NHANES can be found in the Supporting Information, Figure 3.7.

3.3.2 LBATs for a specific cohort

Average longitudinal PCB-153 body burden (ng/g lipid) versus age trends (LBATs) were generated for ten different cohorts born during the period 1900-1990 (Males, see Supporting Information Figure 3.8, Females Figure 3.9). A typical example of these LBATs for males born in 1965-1974 (1970 cohort) is shown in Figure 3.1D (over time period 1985-2050), where different coloured lines represent groups of individuals of different BMI classes. Initially, in 1990, lean individuals (BMI classes underweight and normal) have higher PCB levels than obese individuals (Figure 3.1D). This is primarily due to the dilution effect - lean individuals have less lipid volume, and therefore have higher lipid-normalized PCB-153 body burdens than obese individuals. As the cohort ages, concentrations decline for all BMI classes (because of declining environmental contamination), however, the rate of decline is different among the different BMI classes. For example, PCB-153 declines rather rapidly in individuals within the underweight BMI class over the period 1990-2030 (e.g., apparent elimination half-life as defined by Ritter et al. [21] of 11.0
Figure 3.2: Comparison of model PCB-153 exposure (blue) and NHANES measured PCB-153 concentrations in males (red, ng/g lipid) for birth cohorts 1940-1990 (A-F). Note that this is essentially a CBBT, with the data shown in box and whisker plots.
Contaminant elimination from obese individuals (e.g., class II/III obesity) is much slower (e.g., apparent half-life of 29.9 y for the 1970 male cohort). This results in a “crossing over” of LBATs, wherein obese individuals eventually have higher PCB-153 lipid-normalized body burdens when compared to lean individuals.

The apparent elimination half-life is influenced by two key factors, the rate of decline in environmental contamination (i.e., exposure) and the intrinsic elimination half-life. While the former factor is the same for everyone, the latter is strongly related to an individual’s lipid content (Supporting Information, Figure 3.10). For example, the model calculates an intrinsic elimination half-life of PCB-153 for 1970 cohort males with underweight BMI (over the time period 1990-2030) of 4 y, while it is four times as long (16 y) for those in the class II/III obesity BMI class. Faecal egestion is the main elimination process for highly recalcitrant PCB congeners and it is driven by the contaminant’s fugacity gradient between bodily tissues and gut content. In individuals with a higher lipid content that fugacity gradient is reduced, slowing down elimination.

The “crossing over” of LBATs occurs at different times for individuals of different BMI classes. For example, the LBAT for people in the underweight BMI class crossed over with LBAT for people of normal BMI in the year 1989, but does not cross over with LBAT for people of class II/III obesity until 2000. This can be interpreted by considering the opposing effects of contaminant dilution and differences in elimination rate. In other words, although lean people have higher contaminant elimination rates than obese individuals, they also bear greater body burdens in early adult life (Figure 3.1D). Thus, “crossing over” between LBATs for people of underweight BMI and people of normal BMI occurs much earlier than that between underweight BMI and class II/III obesity because in the first case, elimination rates are greater than contaminant dilution, while in the second case elimination effects are counteracted and delayed by increasingly important dilution effects. By the same arguments we can also explain why “cross-over” between some LBATs occurs at a much later stage (e.g. for people with class I obesity and class II/III obesity). This is because in such cases differences in contaminant elimination are not enough to overcome the dilution effect. Similar observations could also be made for female cohorts (Supporting Information, Figure 3.9).

3.3.3 Cross-sectional body burden versus BMI trends (CBBTs)

The transformation of longitudinal data to cross-sectional data is shown in Figure 3.1D and 3.1E by plotting lipid-normalized PCB-153 concentration versus BMI for one point in time (model results of
individuals of the same BMI class are averaged together, as shown in Figure 3.1D). Figure 3.1E demonstrates that within the same birth cohort, the relationship between PCB-153 body burden and BMI, or CBBT, depends on the sampling year. For example, when the cohort reaches 20 years of age (i.e., in the year 1990) PCB-153 body burden demonstrated a clear negative correlation with BMI (Figure 3.1E, left panel). However, as the cohort ages, this trend is inverted. As the body burden of lean individuals decrease at a faster rate than people with higher BMIs, the CBBT eventually changes from negative to positive (Figure 3.1E). This simulation result is in agreement with the hypothesis of Wolff et al., [50] which states that during periods of declining exposure (i.e., after the 1970s), the body burden for obese people will eventually overtake that of lean people due to slower contaminant elimination from obese individuals.

CBBTs were constructed for six birth cohorts (1940-1990) in multiple different sampling years, from 1960 to 2070 (males, Figure 3.3). Whereas the model predicted clearly negative associations between PCB-153 concentrations and BMI for all birth cohorts in monitoring studies conducted before the 2000s, current and future biomonitoring studies are predicted to reveal more complex relationships. For example, a biomonitoring study conducted in 1990 would find a strong negative correlation between body burden and BMI irrespective of age (e.g., Spearman’s rank correlation $r^s = -0.90$ for the 1970 cohort sampled in 1990). A similar study conducted in 2010 would find a positive correlation between PCB-153 body burden and BMI in older adults (e.g., $r^s = 0.80$ for the 1940 cohort sampled in 2010), little to no correlation for middle-aged adults, while a negative correlation would be observed between body burden and BMI in younger generations (e.g., $r^s = -1.00$ for the 1990 cohort sampled in 2010). However, note that it is the same birth cohorts that continuously have the highest contaminant levels in different sampling years. More specifically, the 1940 and 1950 birth cohorts always have the highest body burdens in biomonitoring studies conducted throughout the 110 year period. This is not surprising because considering the emission profile of PCB-153, which was assumed to have peaked in the 1960s, these cohorts experienced the greatest adult life exposure to the contaminants. This cohort effect (i.e. aging population shifting body burdens to older age groups) was described by Quinn and Wania. [16]

In other words, the model results suggest that in future decades different age cohorts will display different concentration - BMI relationships. In particular, in some birth cohort-sampling year combinations (e.g., 1990 cohort sampled in 2030), those with intermediate BMI are predicted to have higher PCB concentrations than those with either low or high BMI. This again can be interpreted by considering the interaction between dilution effects and elimination rates. First of all, non-negative correlations between body burden and BMI are observed only in older generations because they had more time for differences
in elimination rates between obese individuals and lean individuals to take effect. Secondly, individuals with intermediate BMI display the highest body burden because only they have the appropriate balance between dilution effects and elimination effects required to achieve a high body burden. In other words, people with extremely low BMIs have lost most of their body burdens throughout their lives, while people with extremely high BMIs have very low lipid-normalized body burdens to start with. As a result, those with intermediate BMIs (i.e. those with moderate contaminant body burdens and elimination rates) show the highest body burdens among older populations.

The model results further suggest, that the CBBT can depend on the range of BMIs sampled. Examples are the CBBTs of the 1940 cohort, in particular during sampling years 1980 and 1990 (Figure 3.3). The CBBT in 1980 and 1990 are negative, if the full range of BMI were sampled. However, if the range of BMIs within the sampled cohort were limited to 20 to 30 kg/m$^2$, the observed trend would show no change in PCB concentration with respect to BMI in 1980 or even a positive trend in 1990.

Cohort-specific simulations of CBBTs could serve as a guiding tool for the interpretation of future biomonitoring studies. For example, knowing that CBBTs will depend on the sampling year and birth cohort, future biomonitoring studies could include the age or birth cohort of their test subjects as an independent variable in their studies and avoid potentially confounding factors during their investigation. Again, similar observations were made for females (Supporting Information, Figure 3.11).

### 3.3.4 Effect of biotransformation half-life on CBBTs

In order to evaluate the effect of biotransformation half-life on the shape of CBBTs, we also simulated exposure to PCB-118, -138, and -180 for the 6128 participants. These PCBs have estimated biotransformation half-lives of 8, 25, and 300 years, respectively compared to 35 years for PCB-153. These results, along with PCB-153, are shown in Figure 3.4, for males of birth cohorts from 1940 to 1990, and sampling years from 1960 to 2070 (similar to Figure 3.3) In order to compare the shape of CBBTs directly, all CBBTs were normalized. Unsurprisingly, the CBBTs of PCB-180 were similar to those of PCB-153, due to their similar overall elimination half-lives (which are dominated by faecal egestion). Although the biotransformation half-life of PCB-138 is substantially lower than that of PCB-153, it also displayed very similar CBBTs to PCB-153, again reflecting the similarity in overall elimination kinetics. PCB-118 (biotransformation half-life = 8 years) was the only simulated congener to display some variability in the
shape of its CBBT, indicating that biotransformation has a more substantial influence on overall elimination kinetics. For example, the 1960 cohort sampled in 2020 revealed a positive relationship between PCB body burden and BMI for congeners 138, 153, and 180, while 118 displayed a negative relationship. However, this deviation was only observed for a small subset of birth cohort / sampling year combinations, e.g., sampling years 2010-2040 and birth cohorts 1940-1960. Most of the time, and especially for all CBBTs for the 1970 birth cohort and later, the shape of CBBTs for all simulated congeners were nearly identical. Investigation of PCBs (or other POPs) with biotransformation half-lives $<5$ years (e.g., lower chlorinated PCBs such as PCB-11, a nonlegacy PCB that is produced as a by-product of pigment manufacturing [103]) may reveal significantly different CBBTs. However, they generally contribute little to the overall PCB body burden in humans.

### 3.3.5 Obesity epidemic, aging, and population level body burden

Figure 3.5 shows the population level PCB-153 body burden time trends (A - males, B - females) from 1980 to 2010 under four different scenarios: i) realistic scenario simulated using historical data on population BMI and age distribution; ii) scenario in which no obesity epidemic occurs; iii) scenario where no
Chapter 3. PCB Body Burden and Body Mass Index

Figure 3.4: Comparison of normalized CBBTs for PCB-118 (red), -138 (green), -153 (blue), and -180 (purple), for males. Similar to Figure 3.3, each cohort is shown within subplots in same row, while different sampling years are shown in different columns.
population aging occurs; and iv) scenario in which neither population aging nor obesity epidemic occurs. Reflecting decreasing emissions, repeated cross-sectional sampling of the entire American populations show declining PCB-153 concentrations between 1980 and 2010 for all four scenarios (Figure 3.5). As shown in Figure 3.5B, the onset of obesity epidemic has slightly decreased the average population level PCB-153 body burden for females (from 15.6 ng/g to 15.2 ng/g in 2010), while population aging has increased it (from 13.2 ng/g to 15.2 ng/g, in 2010). This can be interpreted in terms of the dilution effect brought by the obesity epidemic and the cohort effect from the aging population. With the onset of the obesity epidemic in the late 1970s, the lipid-normalized contaminant body burden experiences a decrease because obese people constitute a larger fraction of the total population, causing the population level lipid-normalized body burden to drop. This dilution explanation is consistent with studies on individuals that found a negative relationship between weight gain and POP body burden. On the other hand, population aging means that older cohorts constitute an increasing proportion of the overall population and because older people have higher PCB levels than young ones, the overall population level body burden shifts slightly upwards. As the age effect is greater than the dilution effect (in females), the combined effect of population aging and obesity epidemic is a net increase in population level body burden when compared to the no aging and no obesity scenario (Figure 3.5B). For males (Figure 3.5A), the magnitude of the aging effect is similar to the obesity effect (but in opposite directions). Thus, the real scenario is nearly identical to the combined no aging and no obesity epidemic scenario. Incidentally, in the future, when elimination kinetics become increasingly more important than dilution in controlling the CBBTs, one would expect the obesity epidemic to slow down rather than accelerate further population level declines, i.e. work in concert with, instead of opposing, the aging effect.

The population level trend in the PCB-153 body burden of females (Figure 3.5B) appears to be more affected by both the population aging and obesity epidemic. In general, females live longer than males and as a result there is a higher proportion of older females than older males. This would directly contribute to the greater difference, for females, between the realistic scenario and the no aging scenario, when compared to males. Additionally, this observation may be explained by considering the differences between male and female life cycles. As it is known that breast feeding and giving birth are both processes that decrease the body burden of women during their lifetime, it is possible that these processes could also be responsible for the aforementioned differences in the population level body burden time plots. However, more detailed investigations are needed to ascertain this assumption and whether these differences actually exist. In summary, that the American population on average has both aged and become increasingly obese during the 30-year period is predicted to influence only very...
Figure 3.5: Population level concentrations of PCB-153 (ng/g lipid) for adult US males (A) and adult US females (B) from 1980 to 2010 as calculated using realistic and hypothetical assumptions about the change in BMI distribution and age distribution over that time period.

marginally the time trends obtained from repeated cross-sectional biomonitoring.

3.3.6 Conclusions

This study has highlighted that the sampling year, the range of sampled age classes and the range of sampled BMI classes can all have a strong impact on the CBBTs observed in a HBM study. This can explain the bewildering diversity of CBBTs that have been observed for PCBs and other POPs in different HBM studies. We suggest that mechanistic models such as the ones used here can serve in the development of hypotheses regarding the role of lipid mass in influencing POP concentrations, and facilitate the interpretation of CBBTs in HBM studies. This study suggests that in the future more complex relationships between BMI, PCB-153 body burden and age will likely be observed, and understanding these relationships is imperative in any effort to understand the potential obesogenic effects of POPs. [94] For example, it was shown that for adult males, cross-sectional studies conducted in the future would likely find a positive relationship between PCB-153 body burden and BMI in older cohorts, while a non-monotonic relationship would be observed between body burden and BMI for younger adults. Thus, a recommendation for future HBM studies aimed to investigate the potential obesogenic effects of POPs is to take into account the influence BMI and birth cohorts have on the measured lipid-normalized contaminant concentrations. This study suggests that the influence of the obesity epidemic and population aging on the rate of PCB body burden decline at the population level is only marginal. However, this observation may be different for other POPs with much shorter biotransformation half-lives and time-variant historical emission profiles, e.g., DDT. Furthermore, in the
current study all individuals were assumed to have the same BMI throughout their adult life. Future developments in this modeling approach could include simulations that allow for individual weight loss or weight gain.

3.4 Supporting Information

Figure 3.6: Female growth curves - total body mass (red) and lipid mass (blue) as a function of age for each BMI.
Figure 3.7: Comparison of model PCB-153 exposure (blue) and NHANES measured PCB-153 concentrations in females (red, ng/g lipid) for birth cohorts 1940-1990 (A-F). Note that this is essentially a CBBT, with the data shown in box and whisker plots.
Figure 3.8: Averaged male longitudinal body-burden age trend (LBAT) for each birth cohort 1900-1990. Each coloured curve represents a different BMI class.
Figure 3.9: Averaged female longitudinal body-burden age trend (LBAT) for each birth cohort 1900-1990. Each coloured curve represents a different BMI class.
Figure 3.10: Apparent (red) and intrinsic (blue) elimination half-lives for males (A-D) and females (E-H) from cohorts 1950-1980 over the time period 1990-2030 for PCB-153. Apparent elimination half-lives were calculated by fitting a first-order decay function to the averaged LBATs (Figures 3.8 and 3.9) over the time period 1990-2030. Intrinsic elimination half-lives were obtained from previous calculations in Chapter 2.
Figure 3.11: Comparison of ACC-Human-generated PCB-153 body burden (ng/g lipid) versus BMI (kg/m²) (CBBTs) for females of multiple birth cohorts (1940-1990), by row, and multiple sampling years (1960-2070), by column.

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<th>class II/III obesity</th>
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Table 3.1: Average dietary lipid intake (fish, meat, dairy, and total) among each BMI class. There is no relationship between BMI class and total dietary lipid intake (evaluated by Spearman rank correlation, for all individuals, \( r_s = -0.02 \))
**Table 3.2**: American male age-specific BMI distributions for years 1980, 1990, and 2010. All values in percent.

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b. Derived from Flegal et al. [99]
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Table 3.4: American female age-specific BMI distributions for years 1980, 1990, and 2010. All values in percent.

b. Derived from Flegal et al. [99]
### Table 3.5: American female age distributions for years 1980, 1990, and 2010. All values in percent. Derived from the U.S. Census Bureau Population Estimates. [101]

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<td>13.6</td>
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</tr>
<tr>
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</tr>
<tr>
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Chapter 4

Summary and Outlook

4.1 Brief

The main goal of this thesis was to use a combined mechanistic model of environmental fate and human food chain bioaccumulation to predict PCB exposure for over 6000 participants of a national biomonitoring campaign. Both chapters 2 and 3 examine various aspects of this combined model approach. First, chapter 2 evaluated the ability of the model to accurately reproduce the measured PCB levels in NHANES participants. Secondly, chapter 3 uses the results of chapter 2 to further investigate the role of body mass index and how it influences PCB levels.

4.2 Chapter Summaries

Chapter 2 estimated lifetime PCB exposures for 6128 participants of 1999-2004 NHANES. By using the accompanying questionnaire information from NHANES, the calculation for each participant was individualized (year of birth, sex, body mass index, dietary information, and reproductive behaviour). By using quite a diverse dataset (i.e., large range of ages, dietary preferences, etc.), the ability of the model to reproduce the measured concentration trends with the previously mentioned input parameters is one key way to evaluate model performance. One of the key findings was that the model was able to successfully reproduce PCB concentrations on a population level (i.e., averages), and it was also able to
successfully reproduce measured trends with factors such as age, sex, and parity. However, the model indicated that PCB levels are influenced by dietary intake, the measured data suggests that dietary intake has no impact on PCB levels. One possible reason suggested for this failure was the unreliability of dietary recall studies and food frequency questionnaires. In order to improve individual-specific PCB exposure calculations, one would require much improved and more accurate dietary intake data. Another noteworthy finding from this work was the suggestion that PCB emission histories, which are central to this model approach, be revisited for accuracy.

Chapter 3 takes a closer look at the role body mass index plays and how it influences PCB levels in humans. By taking the individual lifetime exposure results from Chapter 2, we were able to recreate concentration versus BMI relationships for real individuals and real populations from a cross-sectional perspective. The model results were used to investigate the factors that affect the relationship between concentration and BMI. The motivation for this work was a previous hypothesis by Wolff et al. [50] that variable pharmacokinetics between lean and obese people during periods of increasing or decreasing contaminant emissions is responsible for the diverging relationships between contaminant levels and BMI. Our mechanistic modelling approach, using PCB-153 as a model contaminant, did indeed confirm the hypothesis by Wolff et al. More specifically, at first, obese individuals have lower levels because of the dilution effect. However, contaminant elimination processes are slower in obese individuals, and as time progresses, they eventually overtake leaner individuals and have higher PCB levels. We were also able to assess the impact of the obesity epidemic and population aging on the PCB body burden at the population level. Both the obesity epidemic (contributes to lower levels) and population aging (contributes to higher levels) were found to have a marginal impact on population level PCB body burden. Furthermore, the effect of both scenarios combined counteract each other, as the combined scenarios exhibited population level PCB body burden equivalent to the scenario with no population aging nor obesity epidemic.

4.3 Future directions

As highlighted in Chapter 2, improved and more accurate dietary intake data would allow for improved lifetime exposure calculations. In turn, this would improve the estimates of a person’s historical PCB exposure, which would be of great use to epidemiologists, who can use the historical data to investigate possible associations between POP/PCB levels and health outcomes. Chapter 3 is the latest of previous
modelling efforts to analyze in depth the role of various factors and how they influence PCB levels (e.g., age [16], and reproductive behaviour [13]). With improved dietary intake data, perhaps the role of diet and various diet scenarios can be investigated in further depth. For example, biomarkers of energy intake could be used to establish reliable estimates of dietary intake. [104]

The modelling approach described in this thesis should be applicable to many other persistent hydrophobic organic contaminants. Essentially, PCBs are poster child of persistent organic pollutants - they are also the best test case for our modelling exercises because of the abundance of information that exists on PCBs (chemical properties and emission history). Finally, our approach may be preferred when there is a lack of empirical data on time trend contamination in food for the purposes of human exposure modelling - the ability exists to simulate contamination in foodstuffs over a period of multiple decades - in this case, 170 years.
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