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Backward Estimation of Exposure to Organochlorines Using Repeated Measurements

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Great Lakes sport-caught fish are contaminated with various organochlorines (OCs) such as polychlorinated biphenyls (PCBs). Through consumption of these fish, humans are subject to continuing levels of OC contamination. To assess potential adverse effects of past exposure, we compared three different backward extrapolation models. The data originated from OC determinations in a cohort of anglers and their families. Repeated PCB measurements collected in the 1970s, 1980s, and 1990s were used when testing the backward extrapolations. We applied a simple and a complex decay model based on assumptions used in previous studies; a third was a regression model incorporating markers of OC intake and loss. These techniques provided past exposure estimates. Intraclass correlation coefficients (ICCs) were calculated comparing measured and estimated PCB values. ICC values for the regression model equations were 0.77 and 0.89; ICC values for the simple and complex decay models were significantly lower, with ranges of 0.07–0.45 and –0.14–0.69, respectively. Plots showing trends of OC concentrations in fish and humans indicate comparable increases and decreases of PCB in fish and humans, with fish concentrations peaking approximately 10 years before that in humans. Our findings suggest that one should be cautious when using simple backward extrapolation techniques to estimate OC exposure in situations involving changing environmental exposures. Whenever repeated measurements are available, regression analyses seem to produce more accurate backward estimations of exposure. *Key words:* backward extrapolation, epidemiology, exposure assessment, fish consumption, Great Lakes, organochlorines. *Environ Health Perspect* 112:710–716 (2004). doi:10.1289/ehp.6761 available via http://dx.doi.org/ [Online 4 February 2004]

One of the basic steps in the determination of exposure–health associations is exposure assessment. With exposure scenarios, when the inception of disease (onset of disease pathology) has occurred in the past, it becomes necessary to estimate the exposure level during the specific window of time in the past in which disease inception took place. Properties of some contaminants facilitate the use of backward extrapolation to estimate past exposure. One such property is persistence, wherein the concentration of the contaminant in the host is maintained over a defined period of time. If the substance in question is stable and resistant to metabolism, a long exposure half-life will result. With continuing intake, such chemicals will bioaccumulate (Swain 1983). Additionally, bioaccumulated substances will increase when transferred through successive levels of the food chain, a process known as biomagnification. Hence, contaminant concentrations rise as a result of persistence, biomagnification, and bioaccumulation.

Complicating this scenario, however, are initial ignorance of environmental contamination and later intervention to limit the presence of toxicants in the environment. These phases may introduce variations in environmental exposure levels over time. For instance, concentrations of toxicants in human food would follow an increasing trend until regulated, thus resulting in decreasing concentrations. Second, people may vary in their decision to continue using potentially contaminated products. Thus,

backward exposure estimation becomes more difficult because it has to integrate persistence of human body burden (long half-life) and exposure levels in the environment or food that vary over time, as well as the amount and duration of product use over time. One example of this type of scenario is continuing consumption of fish that themselves are characterized by varying polychlorinated biphenyl (PCB) levels. However, regarding persistence, various halogenated organic compounds share similar characteristics.

PCBs possess half-lives ranging from < 1 year up to 71 years and are capable of ascending the food chain and accumulating in human tissues possessing high lipid concentrations (Phillips et al. 1989; Shirai and Kissel 1996; Yakushiji et al. 1984). Exposure to such compounds can take place through accidental environmental contact, dietary intake such as consumption of contaminated food and breast-feeding, and *in utero* (Brown et al. 1994; Guo et al. 1994; Polishuk et al. 1977; Rappolt and Hale 1968; Stewart et al. 1999). Consumption of contaminated food products, such as sport-caught fish, is one of the important exposure pathways for PCBs (Fiore et al. 1989; Humphrey 1983b; Kreiss 1985). Because of persistence, biomagnification, and bioaccumulation, several populations have developed increased body burdens of PCBs [Cordle et al. 1982; Newsome and Andrews 1993; U.S. Environmental Protection Agency (EPA) 1993].

A number of previous studies involving exposures to polyhalogenated compounds have investigated various techniques for the backward extrapolation of past exposure levels. Several toxicokinetic models have been proposed, each of which contains a variety of different assumptions (Needham et al. 1999; Rylander et al. 1998; Weisskopf et al. 2003). All of the proposed models implement various decay constants in the development of their final backward extrapolation model.

A study by Weisskopf et al. (2003) involved the measurement of PCBs in the Great Lakes region. The authors proposed a simple decay model that made use of a single-compartment toxicokinetic model to backward extrapolate PCB exposure due to sport-caught fish consumption. The main assumption of this simple decay model is that subjects will reach an organochlorine (OC) equilibrium faster than OC concentrations in fish change, so the natural decline in body burden or decay of these substances should be estimated based on the decreasing trend of OC concentrations in fish over time (Weisskopf et al. 2003).

Another study extrapolating PCB exposure was conducted in Sweden around the Baltic Sea region. In a more sophisticated model, Rylander et al. (1998) proposed a complex decay model designed to account for yearly reductions in fish OC concentrations, as well as reductions in human PCB concentrations due to periods of lactation.

Our suggested approach, requiring repeated measurements, proposes the use of regression models to predict past exposure to PCBs. Predictors including indicators of changing intake (years and amount of sport-caught fish consumption), indicators of diminution (number of pregnancies, length of breast-feeding), and indicators of a time trend

(years between two PCB determinations) were used in the development of the model.

In this study, we focused on maternal PCB concentrations collected for each of three surveys completed over a 19-year span from 1973 through 1991. We were prompted toward this work because of our interest in adverse reproductive outcomes in the offspring of women who ate fish. Most participants had birth dates between 1950 and 1980. The measurements between 1973 and 1991 do not coincide with the dates of their pregnancies and therefore do not directly reflect the OC concentrations to which their offspring were exposed during pregnancy.

We tested how well the models described above would predict actual OC determinations collected in the past. Repeated OC measurements allowed us to calculate intraclass correlation coefficients (ICCs) comparing actual and estimated values for each of the proposed extrapolation models. This statistic is used to assess how well the backward estimations fit the past OC determinations, thereby determining the efficacy of each model for the backward extrapolation of PCB concentrations involving repeated measurements (Armstrong et al. 1992).

Materials and Methods

Population. In the 1970s, the Michigan Department of Community Health (MDCH) established a cohort of anglers and their families who consumed sport-caught fish, in order to monitor their body burden of PCBs (Humphrey 1983b). To assess the level of PCB contamination in these families due to fish consumption, the MDCH conducted three surveys in 1973–1974, 1979–1982, and 1989–1991, known as the Great Lakes Fish Eaters Studies. MDCH workers recruited anglers and their spouses at sites of fishing activities (e.g., docks, marinas, and bait shops) in 11 Lake Michigan shoreline counties. By the end of the third survey, the cohort totaled 1,177 individuals with PCB determinations, including 419 women.

OC concentrations in fish. In order to determine the degree to which the environmental load of OCs has changed and to compare this change with human data, we gathered information on PCBs in fish from Lake Michigan. Because of similar chemical characteristics and for the sake of comparison, we also collected data on dichlorodiphenyl dichloroethylene (DDE) in fish. PCB and DDE concentrations in fish collected over a range of years were identified through the National Library of Medicine by means of an extensive PubMed literature search [De Vault et al. 1996; Gerstenberger and Dellinger 2002; Great Lakes National Program Office (GLNPO) 2003; Manchester-Neesvig et al. 2001; Neidermyer and Hickey 1976; Veith

1975; Willford et al. 1975]. We were able to identify fish exposure information from 1929 through 1998. The fish used in the determination of PCB and DDE data for the period of 1929 to approximately 1970 were properly stored in formaldehyde or ethyl alcohol. The OC measurements were then conducted in the 1970s. Exposure levels from different Lake Michigan fish species over this time interval were converted into lipid-based concentrations determined by the percentage of fat recorded for each species of fish used in this process. This conversion eliminated the effect of varying fat content in different fish species. An additional reason for lipid-based determinations is that storage in formaldehyde or ethyl alcohol led to dehydrated fish tissues in some historical samples. The values were then condensed into 5-year intervals. The plots representing PCB and DDE fish concentrations were developed by combining PCB and DDE values from separate 5-year intervals. The species of Lake Michigan fish used in the creation of these plots were lake trout, yellow perch, whitefish, white and longnose sucker, and coho and chinook salmon, as well as several prey species such as bloater, alewife, fourhorn sculpin, and rainbow smelt (De Vault et al. 1996; Gerstenberger and Dellinger 2002; GLNPO 2003; Manchester-Neesvig et al. 2001; Neidermyer and Hickey 1976; Veith 1975; Willford et al. 1975). The Michigan Department of Environmental Quality provided additional data for the period 1980–1998.

For the graphs representing time trends in PCB and DDE concentrations in fish, smooth bands were used to indicate levels of exposure in 5-year intervals during the period from 1929 through 1998. Because of the wide variation in PCB and DDE values in different species of fish, a spline routine was used to develop two smooth lines to represent the minimum and maximum levels of PCB and DDE in fish over each time interval. The area between these two lines was then filled in to produce a smooth band that represented the average amount of PCB and DDE contamination in fish over time.

Using external information on fish as a main source of exposure is comparable with the exposure assessment used in other locations, such as Seveso, Italy. Needham et al. (1999) proposed the development of several indices through measurements obtained from source emissions, the environment, and subjects in the chemical plant's surrounding area, around the time of the explosion. We used corroborating data regarding fish contamination to investigate whether the time trend of PCB contamination in sport-caught fish and anglers is comparable.

PCB determinations in human serum. Analyses of serum specimens were performed

by the MDCH Health Risk Assessment Laboratory (Lansing, MI) using a modified Webb-McCall packed column gas chromatography technique to measure serum PCB levels in each study participant. The methodology for this laboratory analysis has been previously reported (Hovinga et al. 1992; Humphrey 1983a; Price et al. 1986). To compare PCB exposures, we used measurements based on the Aroclor 1260 standard that measures the more highly chlorinated PCB congeners. The technical detection limit for PCBs was 3 µg/kg in all three surveys.

Backward extrapolation models. Various assumptions and equations were proposed to account for changes in exposure and reduction of PCBs in the backward extrapolation models (Table 1). We applied these models to determine the extent to which estimated PCB levels concur with PCB concentrations measured in the past.

The decay model of Weisskopf et al. (2003) only included a term for the natural decay of the measured OC exposure. PCB half-lives of 4.6, 8.7, and 11.6 years, corresponding to the suggested decay constants of 0.06, 0.08, and 0.15, were applied.

Rylander et al. (1998) proposed a more complex decay scenario. The authors used different PCB half-lives of 1, 5, 10, 15, and 20 years. Other assumptions were the 25, 33, 50, and 67% loss in PCB body burden at each lactation period, and a yearly reduction of the PCB concentration in fish of 1, 3, 5, 8, and 10%. However, Rylander et al. (1998) did not provide an average intake of PCB from fish. Hence, we additionally included an estimated average PCB intake from fish for each participant based on PCB concentrations in frequently consumed fish (2 µg/ounce), number of servings consumed, an 87% loss in PCB contamination due to trimming and cooking techniques used during food preparation to reduce the amount of fatty tissue consumed (multiplier of 0.13) (Zabik et al. 1995), and an absorption of PCB from fish equal to 50% (Bund/Länder-Arbeitsgruppe Dioxine 1991).

For each of these models, we tested two backward extrapolation equations, one for the period from 1991 through 1979 and one from 1982 through 1973.

Linear regression modeling. Serum samples were collected and PCB concentrations were determined in 1973–1974, 1979–1982, and 1989–1991. We developed two models that regressed participants' PCB determinations from one survey (T) period back to the preceding survey period ($T-1$), whenever measurements for both periods were present. Because of the presence of a skewed distribution for the PCB determinations at the 1989–1991 survey period, $\log_{10}$ PCB concentrations were used for this variable in the

regression modeling. The PCB determinations from the 1973–1974 and 1979–1982 surveys followed normal distributions; therefore, the original PCB concentrations were preserved in the regression modeling. As potential predictors, we employed the PCB concentration at (T), the interval between the two PCB determinations, total years of fish consumption, amount of fish meals consumed, number of pregnancies and lactation periods between two measurements, maternal age, and birth year of the mother. This information was collected in the surveys that accompanied the PCB determinations.

The regression equations were used to calculate the participant's level of PCB exposure for the preceding survey period. We compared the estimated PCB concentration at ($T - 1$) with the measured concentration at ($T - 1$) using the ICC. To achieve a most parsimonious explanatory model, we then used the ICC to determine whether we could eliminate predictors that did not explain the earlier PCB concentrations.

Table 1. Overview of backward extrapolation equations, assumptions, and variables.

Extrapolation equations	Model assumptions and variables
Weisskopf et al. (2003) $(OC)_E = (OC)_M * e^{(\lambda * t)}$	Assumptions *a*) Great Lakes fish PCB concentrations follow first-order kinetics *b*) Fish OC decay constants of 0.06, 0.08, and 0.15 (Weisskopf et al. 2003) Variables: *a*) $(OC)_E$ = estimated OC concentration *b*) $(OC)_M$ = measured OC concentration *c*) $e^{(\lambda * t)}$ = OC decay rate over time t
Simple decay model Estimation of 1980s values from 1990s values $pcb\_80_{(estimate)} = pcb\_90 * e^{[(-\lambda) * t]}$ Estimation of 1970s values from 1980s values $pcb\_70_{(estimate)} = pcb\_80 * e^{[(-\lambda) * t]}$	Assumptions of modified simple decay model *a*) Fish OC decay constants of 0.06, 0.08, and 0.15 (Weisskopf et al. 2003) Variables of modified simple decay model *a*) pcb_90 = measured PCB concentration at 1989–1991 survey *b*) pcb_80 = measured PCB concentration at 1979–1982 survey *c*) $e^{[(-\lambda) * t]}$ = decay rate over time t
Rylander et al. (1998) $(OC)_t = A_{(t)} * (1 - e^{[(-\lambda) * t]})$	Assumptions *a*) 25, 33, 50, and 67% decreases in OC body burden at each lactation period *b*) PCB half-lives of 1, 5, 10, 15, and 20 years *c*) 1, 3, 5, 8, and 10% yearly declines in fish PCB concentrations Variables *a*) $(OC)_t$ = Estimated concentration at year t *b*) $A_{(t)}$ = Steady-state OC concentration in year t *c*) $(1 - e^{[(-\lambda) * t]})$ = OC decay rate over time t
Complex decay model Estimation of 1980s values from 1990s values $PCB\_80_{(estimate)} = PCB\_90 * \beta * e^{[(-\lambda) * t]} - \{[(\epsilon * \delta\_90 * 0.5)/\psi\_80] * \gamma\}$ Estimation of 1970s values from 1980s values $PCB\_70_{(estimate)} = PCB\_80 * \beta * e^{[(-\lambda) * t]} - \{[(\epsilon * \delta\_80 * 0.5)/\psi\_70] * \gamma\}$ $\epsilon = 2 * \sigma * 0.13$	Assumptions of modified complex decay model *a*) 1, 3, 5, 8, and 10% yearly PCB reduction in fish (Rylander et al. 1998) *b*) 25, 33, 50, and 67% loss in PCB body burden at each lactation period (Rylander et al. 1998) *c*) 2 µg PCB/ounce of fish with 87% preparation reduction (Zabik et al. 1995) *d*) 50% PCB absorption from fish (Yakushiji et al. 1984) *e*) PCB half-lives of 1, 5, 10, 15, and 20 years (Rylander et al. 1998) Variables of modified complex decay model *a*) PCB_90 = measured PCB concentration at 1989–1991 survey *b*) PCB_80 = measured PCB concentration at 1979–1982 survey *c*) $e^{[(-\lambda) * t]}$ = decay rate over time t *d*) ϵ = calculated PCB content of fish *e*) δ_90 = participant's mean fish consumption in the 1990s survey *f*) δ_80 = participant's mean fish consumption in the 1980s survey *g*) ψ_80 = participant's weight at 1979–1982 survey *h*) ψ_70 = participant's weight at 1973–1974 survey *i*) β = reduction in body burden due to breast-feeding *j*) γ = yearly reduction of PCB in fish *k*) σ = number of fish servings consumed
Needham et al. (1999) Used age and sex-delineated data to produce accurate exposure indices	Assumptions *a*) OC measurements closest to the event are representative of the OC levels at the time of the event Variables *a*) OC concentrations present in source emissions *b*) OC concentrations in soil samples *c*) Human OC concentrations in surrounding area
Proposed regression model Estimation of 1970s values from 1980s values $PCB\_70_{(estimate)} = pcb\_80 * 0.564 + (\varphi\_80 * -0.163) + (\omega * 0.105)$ Estimation of 1980s values from 1990s values $PCB\_80_{(estimate)} = 10*(-0.193) + (\log_{10} PCB\_90 * 0.780) + (\varphi\_90 * 0.048) + (\eta\_90 * -0.144)$	Assumptions *a*) Mean of the probability distribution for the random error is 0 *b*) Variance of the random error is equal and constant for all values of x *c*) The probability distribution of the random error is normal *d*) Error associated with any two different observations are independent Variables *a*) $PCB\_70_{(estimate)}$ = estimated PCB concentration at 1970s survey *b*) $PCB\_80_{(estimate)}$ = estimated PCB concentration at 1980s survey *c*) PCB_80 = measured PCB concentration in 1980s survey *d*) φ_80 and φ_90 = years between OC measurements *e*) ω = no. of years eating fish before 1st PCB determination *f*) $\log_{10} PCB\_90$ = Log of 1990s survey measured PCB concentration *g*) η_90 = no. of births between 1980s and 1990s OC measurements

Validity of the backward extrapolation models. To estimate agreement, there are several approaches to compare extrapolated values with a gold standard. In our case, the actual PCB measurements are considered to be the gold standard. Correlation coefficients between the estimated values and actual measurements determine whether the rank order within the extrapolations was preserved. However, even if the rank order remains the same, the actual and estimated values could be extremely different; Bland and Altman (1986) suggested using the mean difference plotted over the average of two determinations. Using the ICC combines both of the above approaches (Armstrong et al. 1992). The ICC is defined as

ICC = (Between-subject mean square
 – within-subject mean square)
 ÷ {between-subject mean square
 + [(k – 1)
 × within-subject mean square]}   [1]

The mean squares are derived by dividing each sum of squares by their corresponding degrees of freedom. The ICC shows perfect
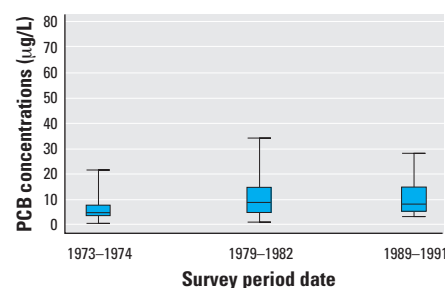

Figure 1. Box plots for the human PCB determinations at each of the three survey periods. The solid line through the box indicates the median PCB concentration for each survey period, and the whiskers indicate the 5th and 95th percentiles for each survey period.

agreement if the estimation equals the measurement for each subject (Armstrong et al. 1992). In this case, the within-subjects mean square (Equation 1) becomes 0 and the ICC is a ratio of two identical between-subject mean squares. A perfect agreement is defined as equal to 1.

To accurately interpret ICC results, it is necessary to have normal distributions for the variables included in the ICC calculation. To fulfill this requirement, we used log-transformed human PCB concentrations from the 1989–1991 survey.

We used the ICC to determine which of the backward extrapolation models predicted the best. For the regression models, we provide the estimated ICC and its lower 5% confidence limit; an upper confidence limit is not defined. For the simple and complex decay models, we calculated ICCs for the various assumptions suggested for the simple and complex decay models and provide ICCs for best- and worst-case scenarios, thus developing a range of ICCs for both extrapolation models. The correlation coefficients provided for each model were used to investigate whether the rank order was preserved. We also calculated absolute differences between estimated and measured PCB values for each extrapolation model.

Linear regression, the decay models, and the calculation of the ICC were performed using SAS statistical software (version 8.02; SAS Institute, Inc., Cary, NC).

Results

OC concentrations in fish and humans. Human PCB determinations presented in Figure 1 show a curvilinear trend. Also, the minimum and maximum PCB concentrations in fish, plotted in Figure 2, show a curvilinear pattern. The peak PCB contamination level in Great Lakes fish (~1970) occurred nearly a decade before the peak PCB concentrations in

Great Lakes fish eaters (1979–1982; Figure 1, Table 2). This may be due to the time it takes for PCB contamination in fish to be biomagnified and passed on to humans. Overall, both the time trends in fish and humans present a corresponding increase that is followed by a decline. In Figure 2, for the sake of comparison, we also included information on trends of DDE contamination in fish.

Characteristics of the female fish-eater population. Of 419 female fish eaters with PCB determinations, 8 were deceased, 120 could not be contacted, 11 gave no consent, and 9 were nuns and were not eligible for the study on reproductive events. This left us with a study population of 271; the proportion of participation is 66.1% (271 of 410). The PCB serum concentrations in female anglers and partners of male anglers increased between 1973 and 1979/1982 and decreased thereafter (Table 2, Figure 1). The average fish consumption went down during this period from 5.0 meals/month to 1.63 meals/month. Two hundred fifty-one women had a pregnancy. However, most of the female fish eaters were born before 1950, and only a few gave birth from 1973 through 1991.

Comparison of backward extrapolation models. The ICCs of the simple decay backward extrapolation were the lowest of the three backward estimation models (ICC for the 1980 values, 0.07–0.39; ICC for the 1970 values, 0.27–0.45; Table 3). When longer half-lives were used in the simple decay model, the resulting estimations provided better predictions, thus increasing the ICC.

The complex decay model based on Rylander et al. (1998) included several assumptions for the reduction of PCBs over time. High levels of PCBs in fish over recent years (1980–1990) led this model to produce several negative estimations for past PCB concentrations. In particular, for the half-life of 1 year, the within-subject mean squares were
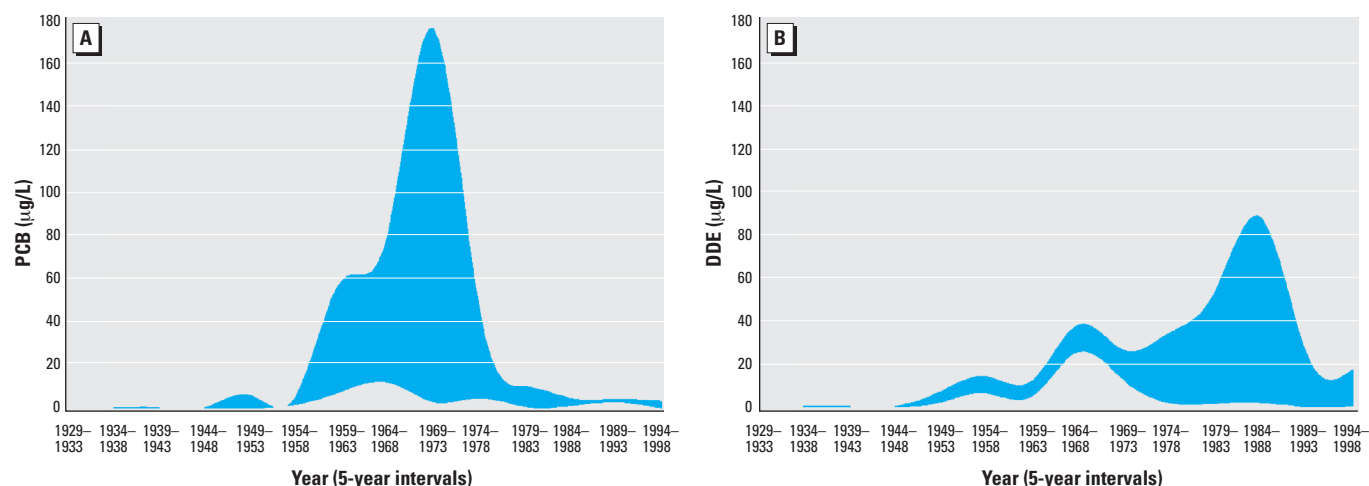

Figure 2. Overall time trends (minimum and maximum values) of PCB (*A*) and DDE (*B*) levels in Lake Michigan fish.

larger than the between-subject variation, which also produced negative ICC values (Table 3). With longer half-lives, the complex decay models revealed a best ICC between 0.43 and 0.69 for estimated 1980 and 1970 values, respectively.

The regression models led to the best fit of estimated and measured PCB values. The backward assessment of estimated values for the 1980s was based on 159 female participants with measurements in both surveys (1989–1991 and 1979–1982). The backward estimation for the 1970s included 22 women with measurements in both the 1973–1974 and 1979–1982 surveys. We identified two halves of a curvilinear trend: increasing PCB concentrations from the 1990s back to the 1980s and decreasing PCB concentrations from the 1980s back to the 1970s. Regression models were used to estimate the two separate portions of the overall curvilinear trend. The resulting equations are presented in Table 1.

Regarding changes between 1989–1991 and 1979–1982, we achieved a good predictive model containing three variables: the log-transformed PCB concentration from the last survey (1989–1991), the length of the interval between the two PCB determinations, and the number of pregnancies that occurred within the two survey periods (Table 1). The PCB levels from 1989–1991 significantly predicted the values in 1979–1982. Pregnancies led to reductions in the estimated PCB concentrations. The time interval showed a positive sign, indicating higher actual PCB values in the 1979–1982 survey compared with that of 1989–1991 (Table 1).

Regarding changes between 1979–1982 and 1973–1974, the most parsimonious model was achieved by including the PCB serum concentrations from 1979–1982, the interval between the two PCB determinations, and the total years of fish consumption until 1973–1974. PCB levels in 1979–1982 were strongly associated with preceding values in 1979–1982. The individual years of fish consumption led to increases in the PCB concentration estimates for 1973–1974. The interval between the two PCB determinations had a negative sign, indicating that the levels were lower in 1973–1974.

The estimated ICCs for the regression models were 0.77 for 1973–1982 and 0.89 for 1979–1991 (Table 3). Even the lower 5% values of the ICC (0.71 for the period from 1982 through 1973, 0.80 for the period from 1991 through 1979) are higher than the best predictions of the two other approaches.

When comparing rank correlations between predicted values and actual measurements, the correlations for the 1979–1982 measurements did not differ substantially (our model: $r_{Spearman} = 0.82$, $p < 0.0001$; simple decay model: $r_{Spearman} = 0.74$, $p < 0.0001$;

complex decay model: $r_{Spearman} = 0.78$, $p < 0.0001$). However, for the backward extrapolation from 1979–1982 to 1973–1974, we found important differences (our model: $r_{Spearman} = 0.91$, $p < 0.0001$; simple decay model: $r_{Spearman} = 0.27$, $p = 0.22$; complex decay model: $r_{Spearman} = 0.12$, $p = 0.61$).

To further investigate the significant correlations for the 1979–1982 measurements, we calculated the differences between estimated and measured values for each of the three backward estimation models (Tables 4 and 5). The least mean difference was detected for the regression model (3.78 µg/L), and the highest for the simple decay model (13.14 µg/L). Additionally, five randomly selected observations along with their measured and estimated

PCB concentrations for this survey period are presented to demonstrate the variability of results obtained through each model.

The estimated values based on the simple decay model, including only a decay component, led to higher concentration estimates for the past. The regression model used to backward extrapolate PCB exposures from 1982 to 1973 was directed toward lower PCB exposure values because the interval between the two PCB determinations had a negative sign (Table 1). Overall, the simple decay model estimated increased PCB concentrations in the past, whereas the regression model indicated predominantly lower PCB concentration estimates for the 1973–1974 survey period.

Table 2. Characteristics of the study population.

Characteristic	No. or frequency	Median (5–95% limit), mean, or percentage
PCB concentration (µg/L; no./median)		
1973–1974	30	5.0 (1.0–22.0)
1979–1982	237	9.1 (1.5–34.6)
1989–1991	178	8.0 (0.0–28.6)
Fish consumption (meals; no./mean)		
1973–1974	27	5.01 (0.0–16.7)
1979–1982	240	2.41 (0.0–8.0)
1989–1991	197	1.63 (0.0–7.3)
Fish consumption (years; no./mean)		
1989–1991	149	33.48 (10.0–70.0)
Maternal age (years; no./mean)		
At birth of child	251	29.41 (21.0–39.0)
Birth year of the mother (frequency/percentage)		
Before 1930	71	28.2
1930–1939	61	24.2
1940–1949	79	31.4
1950 and after	41	16.2
No. of pregnancies (frequency/percentage)		
1973–1974 to 1979–1982		
0	170	98.2
1	2	1.2
2	1	0.6
1979–1982 to 1989–1991		
0	158	91.3
1	11	6.4
2	4	2.3
No. of breast-feeding periods (frequency/percentage)		
1973–1974 to 1979–1982		
0	171	98.8
1	1	0.6
2	1	0.6
1979–1982 to 1989–1991		
0	158	91.3
1	9	5.2
2	6	3.5

Table 3. Calculated ICCs for proposed models.

Extrapolation equations	ICCs
Simple decay model (minimum–maximum)	
Estimation of 1980s values from 1990s values	0.07–0.39
Estimation of 1970s values from 1980s values	0.27–0.45
Complex decay model (minimum–maximum)	
Estimation of 1980s values from 1990s values	⁻0.12–0.69
Estimation of 1970s values from 1980s values	⁻0.14–0.43
Proposed regression model	
Estimation of 1980s values from 1990s values	0.89 (lower 5% limit, 0.80)
Estimation of 1970s values from 1980s values	0.77 (lower 5% limit, 0.71)

To predict the PCB concentration in women at the time of delivery, we used different time factors (decay constants, half-lives, or regression factors) in the projected models (Table 1) and multiplied these with the time difference between the participant's last PCB determination and their date of birth. These products were then plotted against the calendar period (Figure 3). Figure 3 includes the original PCB measurements from the three survey periods completed from 1973 through 1991 and the PCB values predicted by the simple decay model and by our regression model for each participant's date of birth.

The three repeated human PCB concentrations and the PCB concentrations collected in fish were used to develop graphs to represent trends in human and fish PCB levels over time (Figures 2 and 3).

Discussion

Exposure assessment using backward extrapolation can result in extremely different estimations. Persistent chemicals, such as PCBs, have the characteristic of long half-lives. However, changes in environmental conditions and subsequent changes in intake can result in misleading exposure assessments when relying solely on current measurements and persistence. Our setting focuses on fish contamination in the Great Lakes and corresponding PCB levels in anglers and their spouses. PCB fish contamination was low from 1920 through 1950, increased dramatically thereafter, and declined again in the 1970s (Figure 2). Using measurements from the 1990s, a simple decay model leads to large overestimations of past exposures (Weisskopf et al. 2003). The backward exposure assessment that employed changing fish PCB levels and reduction due to breast-feeding as proposed by Rylander et al. (1998) produced an acceptable fit in the presence of long half-lives. Our regression model based on repeated measurements leads to the best overall PCB estimations at each survey period.

For the period between 1979 and 1991, our model is based on PCB concentrations from 159 female fish eaters with determinations in both surveys. However, a limitation of our results is the limited number of repeated measurements comparing the 1970s with later measurements in the 1980s (*n* = 22). It may be that these 22 women do not represent changes typically found between 1970 and 1980. However, we have also found a similar trend in male fish eaters (Karmaus et al. 2002).

Using correlation coefficients comparing estimated values and actual measurements, we would not have identified differences for the backward estimations for 1979–1982. Nevertheless, large disagreements were discovered through comparing absolute differences for each model (Table 4). This discrepancy was explained in 1986, when Bland and Altman (1986) showed that, although correlations are significant and rank orders are preserved, this does not mean that the estimated and measured individual values will be comparable. The results show that the ICC is superior in determining agreements because it takes both correlation and difference into account.

For the backward estimations for 1973–1974, the rank orders for the simple decay and the complex decay model are not preserved (simple decay model: $r_{Spearman}$ = 0.27, p = 0.22; complex decay model: $r_{Spearman}$ = 0.12, p = 0.61). The reasons for this are that the actual measurements were lower before 1979 (Figure 1) and both decay models resulted in higher backward estimates, illustrated for the simple decay model in Figure 3.

The results show that we estimated two different trends, an increase in PCB concentrations from 1973 through 1982, and a decrease from 1979 through 1991. For our regression-based backward assessments, the comparison of PCB concentrations presented in Figures 2 and 3 suggests a similar trend between fish and humans. There is an increase in PCB exposure concentrations closely followed by a corresponding decrease in PCB exposure levels. This is suggestive of PCB fish concentrations being transferred up the food chain and resulting in similar trends in humans, however, with a delay of approximately 10 years. We did not include changing fish concentrations in our models. However, the trend in PCB concentrations in fish as an external criterion supports our findings of suggested lower human levels in the past. Rylander et al. (1998) also incorporated declines in fish concentration in the range of 1–10%; however, the PCB levels in Lake Michigan fish indicate a much stronger decline of approximately 90% since the 1970s (Figure 2).

Based on the ICC values calculated for the simple decay model (Table 3), we suggest that this type of model is too simple to obtain an accurate backward estimation of OC contamination in humans. This approach does not contain variables necessary to model changes in OC concentrations in the environment, such as fish contamination levels or consumption of sport-caught fish.

The proposed linear regression modeling for the backward extrapolation of OC exposure turned out to be an accurate method for an exposure scenario with changing environmental conditions (ICC, 0.77–0.89; Table 3). The modeling employs repeated measurements and uses potentially necessary predictors

Table 4. Absolute values of the mean difference (measured – estimated) calculated for each of the backward extrapolation models.

Model	PCB concentrations (µg/L)		
	Mean difference	Lower 5% limit	Upper 5% limit
Simple decay model	13.14	1.50	44.75
Complex decay model	6.62	0.45	22.13
Regression model	3.78	0.08	11.69

Table 5. Five randomly selected examples of measured PCB concentrations from the 1979–1982 survey compared with estimates calculated through the various backward extrapolation approaches.

No.	PCB concentrations (µg/L)			
	Measured	Simple decay model[a]	Complex decay model[b]	Regression model
1	20.2	39.88	26.87	18.88
2	68.1	172.76	119.00	46.28
3	5.2	12.24	−0.349	6.38
4	15.9	42.48	21.77	15.53
5	7.3	22.53	5.42	8.71

[a]Half-life = 11.5 years. [b]Half-life = 20 years; 67% loss at each lactation; 10% yearly PCB reduction in fish.
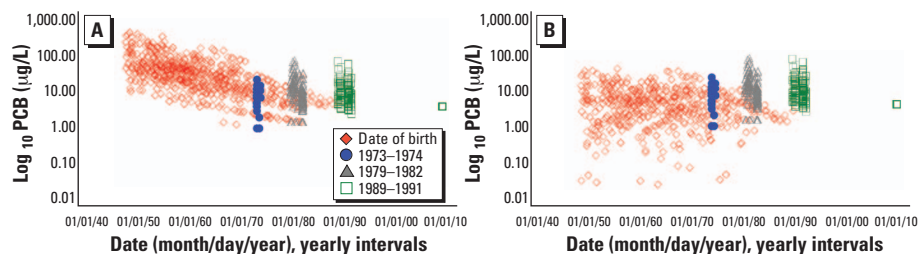

Figure 3. PCB concentration estimates calculated over time for the (*A*) simple decay and (*B*) regression models based on concentration estimates for each participant at their date of birth compared with the actual PCB determinations collected over the three survey periods.

needed to properly backward extrapolate exposure.

We focused primarily on PCB concentrations in women to model potential exposure levels to which their offspring may be exposed *in utero*. One limitation of our suggested approach is that the entire basis of the regression model is dependent on having repeated measurements. Without availability of repeated measurements, the complex decay model (Rylander et al. 1998) would generate better results than the simple decay model. Additionally, the complex decay model may be improved by employing measurements that reflect time trends determined in other environmental entities specific to the region of study.

Because other OC exposures such as DDE have properties similar to those of PCBs and also have similar exposure trends in Great Lakes fish (Figure 2), they may also be backward extrapolated through regression modeling.

Conclusion

Backward extrapolation models can provide varying results depending on the assumptions used. We recommend validating backward extrapolation models with past exposure measurements before applying estimated exposure levels in assessment of human health effects. Our results indicate that when repeated exposure measurements are available, backward estimations based on regression models are superior. Results of the simple decay model do not seem acceptable, whereas a complex decay model generated satisfactory results when employing longer half-lives. To obtain valid backward estimations of past human exposure in the absence of repeated measurements, we recommend the use of a complex decay model following the strategies that Rylander et al. (1998) have established through prior analyses. We suggest improving the model by not only including declines in fish PCB concentrations or other environmental toxicants but also by taking into account any variations that can be identified through environmental or food measurements.

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The author wrote this letter in his capacity as chairman of the Toxicology Research Task Group of the Phthalate Esters Panel, a trade association representing the phthalate industry. He certifies that his freedom to design, conduct, interpret, and publish research was not compromised by any controlling sponsor as a condition of review and publication.

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Editor's Note: In accordance with journal policy, we attempted to contact Osvaldo Rosario, the corresponding author, to ask whether he wanted to respond to this letter, but our attempts have not been successful.

Correction

Karmaus et al. detected errors in their article "Backward Estimation of Exposure to Organochlorines using Repeated Measurements" [Environ Health Perspect 112:710–716 (2004)]. In Table 1, values in the equations for the proposed regression model were incorrect. The correct equations for Table 1 are as follows:

For estimation of 1970s values from 1980s values,

$$PCB\_70_{(estimate)} = PCB\_80 * 0.565 + (\varphi\_80 * -0.163) + (\omega * 0.106)$$

For estimation of 1980s values from 1990s values

$$PCB\_80_{(estimate)} = 10^{[-0.193 + (\log_{10} PCB\_90 * 0.781) + (\varphi\_90 * 0.049) + (\eta\_90 * -0.145)]}$$

Also, in Figure 3, there should not be a measurement for the year 2010.
The authors appologize for the errors.