# Assessment of exposure to PCB 153 from breast feeding and normal food intake in individual children using a system approach model

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## Abstract

Investigators have typically relied on a single or few discrete time points as measures of polychlorinated biphenyl (PCB) body burden, however health effects are more likely to be the result of integrative exposure in time, optionally expressed as an area under the time curve (AUC) of PCB serum concentration. Using data from a subgroup of 93 infants from a birth cohort in eastern Slovakia—a region highly polluted by PCBs—we fit a system type model, customized to our longitudinal measures of serum PCB concentrations in cord, 6, 16, and, 45 month blood specimens. The most abundant congener, PCB 153, was chosen for modeling purposes. In addition to currently used methods of exposure assessment, our approach estimates a concentration time profile for each subject, taking into account mean residence time of PCB 153 molecules in the body, duration of breast feeding, hypothetical PCB 153 concentration in steady-state without breast feeding and alternately without normal food intake. Hypothetical PCB 153 concentration in steady-state without normal food intake correlates with AUC (r=0.84, p<0.001) as well as with duration of breast feeding (r=0.64, p<0.001). It makes possible to determine each subject's exposure profile expressed as AUC of PCBs serum concentration with a minimum model parameters. PCB body burden in most infants was strongly associated with duration of breast feeding in most, but not all children, was apparent from model output.

## Keywords

Polychlorinated biphenyls; Breast feeding; Toxicokinetics; Modeling; Mean residence time; Children

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## 1. Introduction

Polychlorinated biphenyls (PCBs) are a member of the organochlorine family, and though they are no longer produced, they are still found in the environment and in numerous wildlife species, as well as human tissues. Human exposure to PCBs first occurs *in utero* through transplacental transfer of PCBs from mother to infant. After birth, infants are exposed to PCBs via breast feeding, and later through intake of contaminated foods. To assess the association between PCB exposure and health outcomes, investigators have typically relied on discrete time points as a measure of PCB body burden. Examples include PCB concentrations measured in maternal blood taken during pregnancy (Chevrier et al., 2008; Darnerud et al., 2010; Glynn et al., 2008; Hertz-Picciotto et al., 2008; Lopez-Espinoza et al., 2009; McGlynn et al., 2009; Roze et al., 2009; Terrell et al., 2009; Wilhelm et al., 2008), cord blood (Brucker-Davis et al., 2008; Dallaire et al., 2006; Otake et al., 2007; Sagiv et al., 2010; Tan et al., 2009), placental tissue (Laisi et al., 2008; Reichrtova et al., 1999; Wang et al., 2005), breast milk (Darnerud et al., 2010; Glynn et al., 2008; Heilman et al., 2006), or PCB concentrations measured postnatally in the blood of infants and children (Barr et al., 2006; Darnerud et al., 2010; Grimalt et al., 2010; Sunyer et al., 2008). While these exposures are correlated across time, they may not accurately reflect PCB body burden for several reasons. First, the likelihood of PCB toxicity from a particular exposure scenario may be most strongly related to the maximum concentration ($C_{max}$) of PCBs in the target tissue (i.e. a "peak" exposure), or a cumulative measure of PCBs over time. Second, estimating a maximum concentration or "peak" exposure is difficult in most longitudinal studies since few PCB concentrations are determined, and often, these determinations are spaced widely in time. Finally, calculating a cumulative measure of PCB exposure (a widely used metric for such an exposure scenario is the "area under the concentration curve" (AUC)) also requires serial measures of PCB concentration in the developing infant and child. Complicating the issue of assessing exposure is that for developmental effects, the chemical time course may also have to coincide with the window of susceptibility for a particular gestational or postnatal event (Young et al., 1996), leading to situations where either AUC or $C_{max}$ or the levels within a narrow time window may be the more appropriate dose metric (Verner et al., 2010)..

With the aim of examining several developmental health outcomes in relation to PCB exposures occurring during pregnancy and into postnatal life, we launched a birth cohort study of mother-infant pairs (Hertz-Picciotto et al., 2003) living in an area of eastern Slovakia with significant environmental contamination (Kočan et al., 1994). The objective of this work was to use longitudinally obtained measurements to develop more useful exposure metrics which could be applied to evaluate exposure-outcome associations.

## 2. Materials and methods

### 2.1 Study subjects

A cohort of mothers with newborns was recruited from 2 regions of eastern Slovakia as described elsewhere (Hertz-Picciotto et al., 2003; Sonneborn et al., 2008b). Information on breastfeeding was collected using questionnaires administered during follow up visits at 6, 16, and 45 months of age.

### 2.2 Analyses

Blood samples from children were collected from umbilical cord and at 6, 16 and 45 months of age by a trained nurse using venipuncture. Samples were stored in a refrigerator and within 2 hours transported to the Biochemical Department, where they were centrifuged and serum aliquots were divided into test tubes. Blood sera were stored frozen at −18°C until

transport to the Slovak Medical University for PCB analyses. Written informed consent was obtained from parents. The study was approved by the Ethics Committee of the Slovak Medical University. The concentration of 15 PCB congeners (PCB IUPAC #28, #52, #101, #105, #114, #118, #123, #138, #153, #156, #157, #167, #170, #180, and #189) were determined in the sera samples by high-resolution gas chromatography with electron capture detection (Čonka et al., 2005; Kočan et al., 1994). Total serum lipids were estimated using enzymatic summation method (Akins et al., 1989). Funding permitted to complete all chemical analyses except 93 serum samples taken at the age of 6 months.

### 2.3 Model description

The lipid adjusted serum concentration of the most abundant PCB congener, #153, was used for modeling the time-course of PCB concentration. The measured PCB concentration after birth C(t), can be described by the relationship:

$$C(t) = C(0) + \Delta C(t) \tag{1},$$

where t is time, $C(0) = C_0$ is PCB concentration at birth and $\Delta C(t)$ is an increase of PCB concentration given by environment, mainly by breast feeding with a transfer rate $I_{bf}$ and normal food intake with a transfer rate $I_f$ (index bf means breast feeding and f food).

Suppose that the principle of superposition holds for system W studied (Figure 1a), we can describe the function $\Delta C(t)$ by convolution of the weighting function of the system of the child W(t) and function of effect of PCB I(t):

$$\Delta C(t) = W(t) \otimes I(t) \tag{2}$$

It holds for function I(t) (Figure 1b):

$I(t) = I_{bf}$ for $t < t_{bf}$ and $I(t) = I_f$ for $t > t_{bf}$, where $t_{bf}$ is duration of breast feeding.

By means of Laplace transform (Debnath, 1995) we can write for $\Delta C$ the equation

$$\Delta C(s) = H(s)I(s) \tag{3},$$

where s is Laplace operator and H(s) is transfer function of the system PCB concentration increase of the child $\Delta C$ depending on rate of PCB I(t).

Due to small number of measured PCB serum concentrations after birth, we apply to system studied the simplest model in form of the transfer function

$$H(s) = \frac{G}{MTs + 1}$$

where G, gain of the system, is a parameter that characterizes the static properties of the system in steady state and MT (mean time) is a parameter that characterizes the dynamic properties of the system (Dedík and Ďurišová, 1999). The value 1/G is clearance of the system. Knowing values of $t_{bf}$, $I_{bf}$, $I_f$ and the measured PCB concentrations, the values of G and MT of the model studied could be assessed in a similar way as previously (Dedík et al., 1997).

As we do not know values of $I_{bf}$ and $I_f$, we cannot estimate the gain of the system G from the measured PCB concentration-time profile and from data on duration of breast feeding $t_{bf}$. We have to consider the value of parameter G equal one and the transfer function of model as

$$H(s) = \frac{1}{MTs+1}$$

(4)

With respect to this we cannot estimatee clearance of the system and instead of values $I_{bf}$ and $I_f$, we can assess only the limit PCB serum concentration values for the limiting case of permanent breast feeding, $t_{bf} \rightarrow \infty$ as

$$C_{bf_\infty} = C_0 + \Delta C_{bf_\infty} \text{ in time } t \rightarrow \infty$$

and without breast feeding $t_{bf} = 0$

$$C_{f_\infty} = C(0) + \Delta C_f - \Delta C_{bf} \text{ in time } t \rightarrow \infty$$

Instead of function I(t) we shall consider for entering function of the system the function L(t) for which it holds:

$$L(t) = \Delta C_{bf_\infty} \text{ for } t \leq t_{bf} \text{ and } L(t) = \Delta C_f - \Delta C_{bf_\infty} \text{ for } t > t_{bf}$$

For analytical solution of the model $\Delta C(t)$ then holds

$$\Delta C(t) = \Delta C_{bf_\infty}(1 - e^{-\frac{t}{MT}}) \text{ for } t \leq t_{bf} \text{ and}$$

(5)

$$\Delta C(t) = \Delta C_{bf_\infty}(1 - e^{-\frac{t}{MT}}) + (\Delta C_{bf_\infty} - \Delta C_{f_\infty})(1 - e^{-\frac{t-t_{bf}}{MT}}) \text{ for } t > t_{bf}.$$

(6)

Figure 2 illustrates equations (1), (5) and (6).

Vector $\lambda$ of estimated model parameters will then be:

$$\lambda = (MT, \Delta C_{bf_\infty}, \Delta C_{f_\infty})$$

The parameters of vector $\lambda$ were assessed by Monte Carlo simulations.

## 3. Results

Statistics on concentration of PCB 153 in cord blood serum $C_0$ and at 6, 16 and 45 months of age ($C_6$, $C_{16}$ and $C_{45}$, respectively) and duration of breast feeding $t_{bf}$ are shown in upper part of Table 1. The concentration data for all time intervals were positively skewed and lognormally distributed (one-sample Kolmogorov-Smirnov Test). The following weight increase in g in children of our cohort has been observed (means±SE): birth weight 3277.87±486.93, 6 months 7791.78±1098.81, 16 months 11802.13±1508.45 and 45 months 17241.94±2986.03.

The capability of the suggested model to describe the PCB 153 serum concentration in infants with various duration of breast feeding can be seen from Figure 3. The model describes well the PCB 153 serum concentration and at the time of weaning the massive uptake of PCB 153 ceased which was reflected by the onset of serum PCB 153 decrease.

Figure 4 is showing PCB 153 measured serum concentrations and the calculated approximations for 12 infants with equal duration of breast feeding of 16 months and rank ordered according to the estimated MT. It can be seen that in the 2 children in which the concentration increased after weaning, the longest MTs, 108 and 134 months, were observed. The kinetics of PCB 153 serum concentration of each child was described by parameters MT, $C_{bf,\infty}$ $C_{f,\infty}$ and AUC (Table 1 lower part). The individual values of $C_{bf,\infty}$ and $C_{f,\infty}$ were normalized with regard to $C_0$ in order to illustrate better the kinetics of PCB 153 in the body.

Spearman's correlations in Figure 5 show that $C_{bf,\infty}$ is related to AUC (Figure 5a: r=0.84, p<0.001) and that $t_{bf}$ predicts AUC (Figure 5b: r=0.86, p<0.001), $C_{bf,\infty}$ (Figure 5c: r=0.64, p<0.001), $C_{bf,\infty}/C_0$ (Figure 5d: r=0.85, p<0.001), $C_{f,\infty}$ ( Figure 5e: r=0.78, p<0.001) and $C_{f,\infty}/C_0$ (Figure 5f: r=0.78, p<0.001). MT was related to AUC (r=0.6, p<0.001), $C_{bf,\infty}$ (r=0.55, p<0.001), $C_{bf,\infty}/C_0$ (r=0.71, p<0.001), $C_{f,\infty}$ (r=0.60, p<0.001) and $C_{f,\infty}/C_0$ (r=0.59, p<0.001). The ratio $C_{bf,\infty}/C_{f,\infty}$ for 89 infants was >1, only for 4 infants the build up of PCB 153 body burden via normal food intake was greater than via milk. The model enables estimation of an AUC for each individual child. To demonstrate this, AUC values were calculated for increasing time for 4 children with largely varying duration of breast feeding (Figure 6).

## 4. Discussion

The children of our cohort have been born with widely varying concentrations of PCB 153 in serum, which is reflected by the nearly 9-fold ratio of the 95th to the 5th percentiles of PCB 153 concentration. This compares well to a report summarizing 10 earlier studies which showed a range of ratios from 3.8 to 12.3 with a median of 7.5 (Longnecker et al., 2003).

The developed model approximating PCB 153 in the body of infants belongs to the category of "system models" in distinction to the "deterministic pharmacokinetic models" (Ďurišová and Dedík, 2005) and helps the analyst to understand the functionality of the system. The good fit of the model to our data, confirmed by Akaike's criterion value (Yamaoka et al., 1978), indicates that PCB very probably behaves in the body of our children in a single phase and with regard to its lipophilicity presumably in the body fat and its elimination kinetics is of first order. Our model assumes instant mixing of PCB 153 in the body and distribution into fat, linear response to changes in dose and constant intake rate during breast feeding, recently confirmed (LaKind et al., 2009). From model equations and model parameters of each subject we can calculate AUC for each child for selected time limits. Recently this approach was applied, using a physiologically based pharmacokinetic model, in a study of neurobehavioral performance in children (Verner et al., 2010). Thus the model developed here gives an opportunity to relate the health outcomes of each participant to their own individual PCB 153 exposure profile.

Our results differentiating between PCB exposures due to breast feeding and normal food intake in individual infants based purely on serial PCB serum concentration measurements, complement data of others in this direction. Direct comparison is uneasy as some authors base their estimates besides concentration measurements on inherent model assumptions or do not treat PCBs in their prediction but related polychlorinated dibenzodioxins,

polychlorinated dibenzofurans or mixtures of congeners. First to be mentioned are the single time point predictions of PCB serum concentrations: Ayotte et al., (2003) explained 72% of PCB-153 plasma concentration variance at 6 months postpartum using a multivariate model that included maternal PCB 153 plasma lipid concentration, breast feeding duration, and the sum of two skin-fold thicknesses. Jacobson et al., (1989) studied determinants to PCB plasma concentration in 4-year old children and found that maternal PCB milk level and breast feeding duration jointly explained 60% of the variance. The PCB levels in cord blood and human milk and the duration of breast feeding explained the 75% variance of the plasma PCB level at 42 months (Lanting et al., 1998). In another study (Patandin et al., 1997) the duration of breast feeding, breast milk PCB concentration, and the child's weight showed statistically significant associations with the child's plasma lipid concentration at 3.5 years of age. Next are several studies where the PCBs body burden was modeled as a continuous variable in contrast to single time point prediction. In an earlier paper body burden of dioxin-like compounds in Inuits from birth to age 75 years was calculated using a physiologically based pharmacokinetic (PBPK) model (Ayotte et al., 1996). A similar approach and maternal blood levels made possible to predict PCB concentrations in infant blood, breast milk and cord blood (Verner et al., 2009). Our data can less easily be compared with those derived to assess exposure to polychlorinated dibenzodioxins, polychlorinated dibenzofurans or dioxin-like compounds (Kerger et al., 2007; Kreuzer et al., 1997; LaKind et al., 2000; Lorber and Phillips, 2002; Patandin et al., 1999).

A few limitations of our approach should be mentioned. First, the current model does not take into account the role of specific food sources. In an earlier work (Sonneborn et al., 2008a), we have shown that consumption of locally produced pork and other fatty foods resulted in higher concentrations of PCB levels in the mothers, as compared with those who purchased such foods from retail stores. It is possible, therefore, that these same foodstuffs might affect the child's PCB levels as well. This might, in fact, explain the curves of those children where PCBs continued to rise after weaning. Secondly, possibly as a consequence of variability in food types consumed (specifically, amount of fat) and in the sources of those foods, the extreme variability in estimated model parameters might be overestimated. In other words, the implicit assumption of our model is that normal food consumption is uniform across the study population. Elaborating our model might narrow the range of parameter estimates.

MT is a basic model parameter in biological and technical disciplines for description of first order linear systems by first order differential equations with constant coefficients and their solution in time. It is the average time a substance spends within a specified region of space and its potential for concentration-effect assessments is obvious. It is visualized in Figure 2 as a tangent to response intersecting the baseline at t=0 (Buffham and Kropholler, 1973). In specified settings it is a measure of the rate of elimination of a xenobiotic (Karol, 1990; Veng-Pedersen, 1989a; Veng-Pedersen, 1989b). In our scenario the parameter MT reflects the rate at which the body of the child handles PCB 153 reflecting a large scale of mechanisms, including increasing fat content. Thus the greater the rate of PCB 153 serum decrease is, the smaller is the MT value. MT besides other factors may be related to activity of enzymes metabolizing PCB. We reported about high variability of PCB metabolism processes in humans (Hovander et al., 2006; Linderholm et al., 2007; Park et al., 2007; Park et al., 2008). The hypothesis whether MT is related to expression of enzymes metabolizing PCB in children, for which considerably shorter apparent half lives compared to adults were reported (Milbrath MD et al., 2009), has to be examined.

## 5. Conclusions

The need to compare health outcomes observed in children of our cohort, characterized by relatively high and variable PCB body burdens, with time integrated individual PCB exposures, prompted us to develop an original approach 1. customized to our time series concentration data, 2. differentiating between breast feeding and normal food PCB intake and 3. characterizing each subject's toxicokinetic profile with a minimum model parameters enabling calculation of an area under the time curve of PCB serum concentration.

- Serum PCB 153 was determined serially in infants from birth to 45 months

- So far published PCB exposure assessments did not suite our longitudinal study design

- Original model fitted to data describes kinetics of PCB in each subject individually

- Mean residence time of PCB molecules in the body and AUCs were evaluated

- It is differentiated between PCB intake by breast feeding and normal food intake

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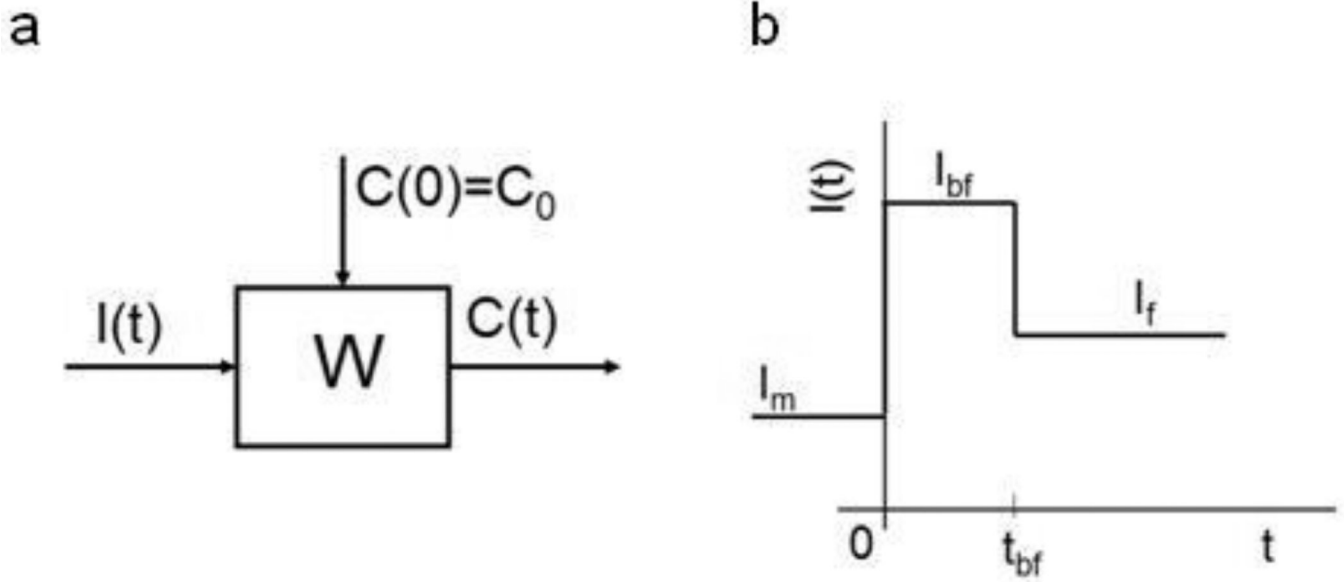
a

$$C(0)=C_0$$

$I(t) \longrightarrow \boxed{W} \longrightarrow C(t)$

b

**Figure 1.**
a: Definition of system W. I, C is the input respectively the output function of the system. C(0) - Initial condition of system, t- time. b: Time course of input function I(t), where t is time, $I_m$, $I_{bf}$ and $I_f$ are hypothetical transfer rates of PCB from mother to fetus, from mother milk to infant and from normal food to infant, respectively. $t_{bf}$ is duration of breast feeding.
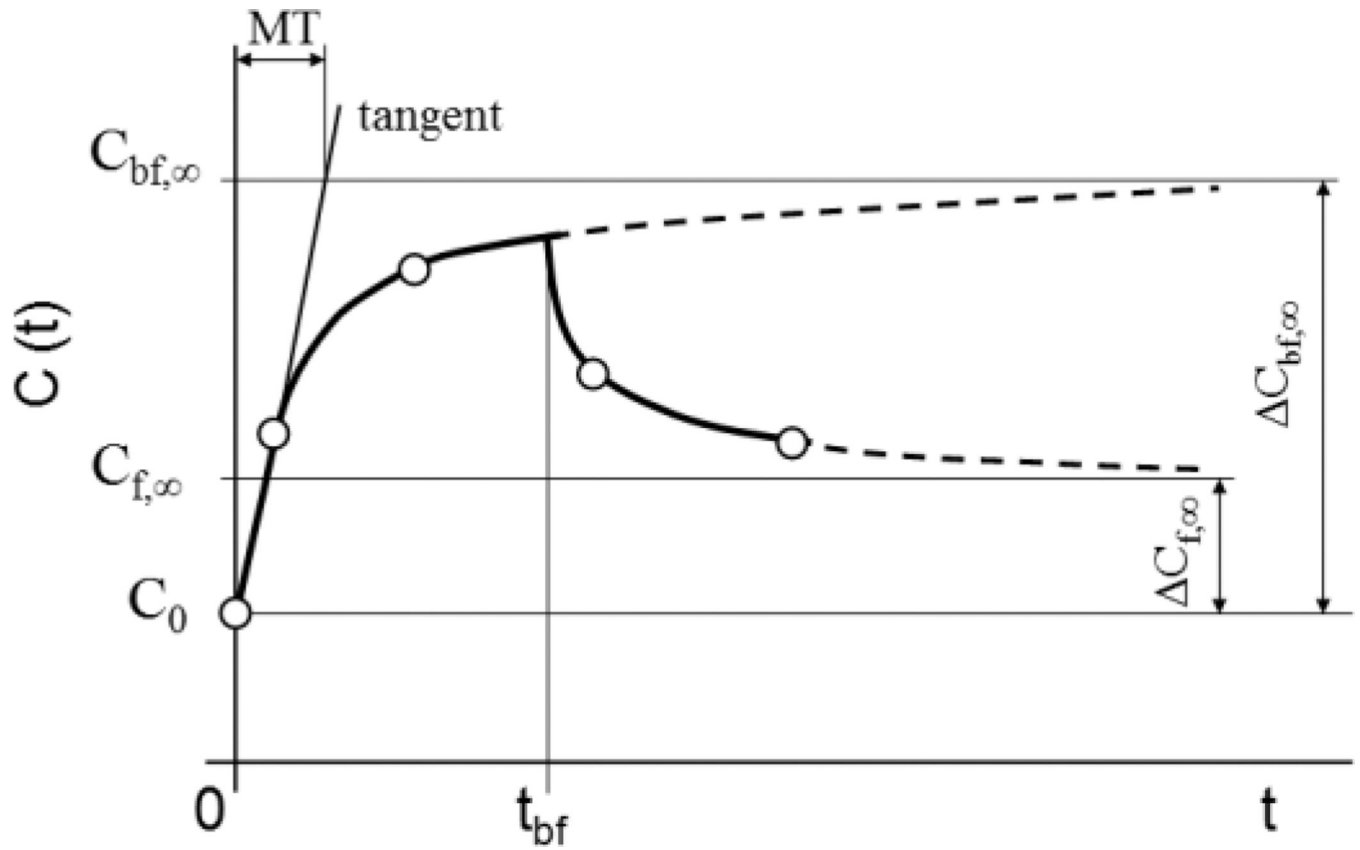
**Figure 2.**
Illustration of system output function C(t), where t is time, and of the model parameters used for approximation of the concentration of PCB in serum of infants. $t_{bf}$ is duration of breast feeding, $C_{bf,\infty}$ is a hypothetical limit value of PCB concentration increase for t and $t_{bf}$ converging to infinity and $C_{f,\infty}$ is a hypothetical limit value of PCB concentration increase for t converging to infinity and $t_{bf}$ converging to zero and MT is mean time of PCB in the body of infants.
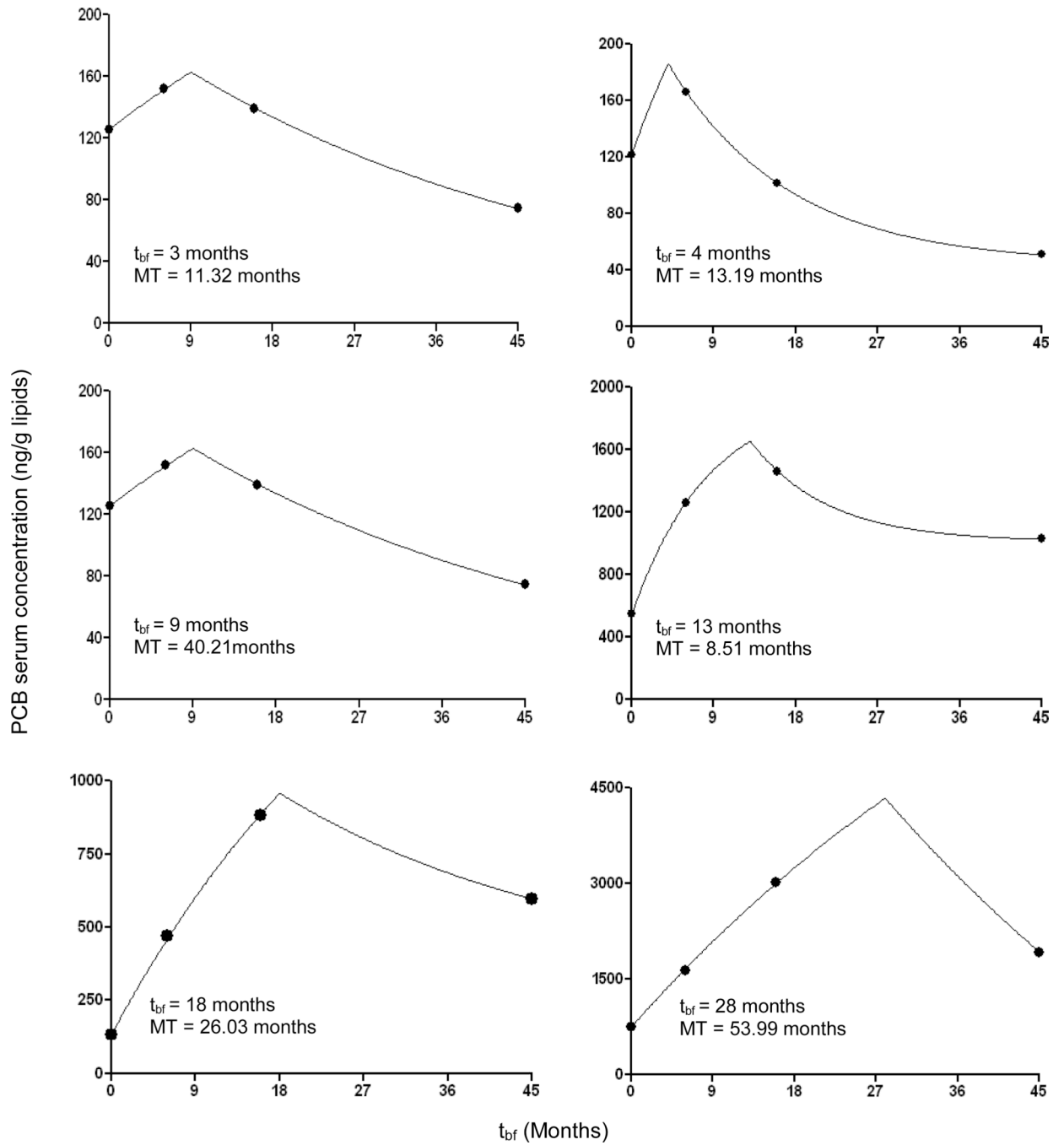
**Figure 3.**
The measured PCB 153 serum concentrations and the calculated curve for six children with markedly different duration of breast feeding $t_{bf}$. Note the markedly different vertical scales.
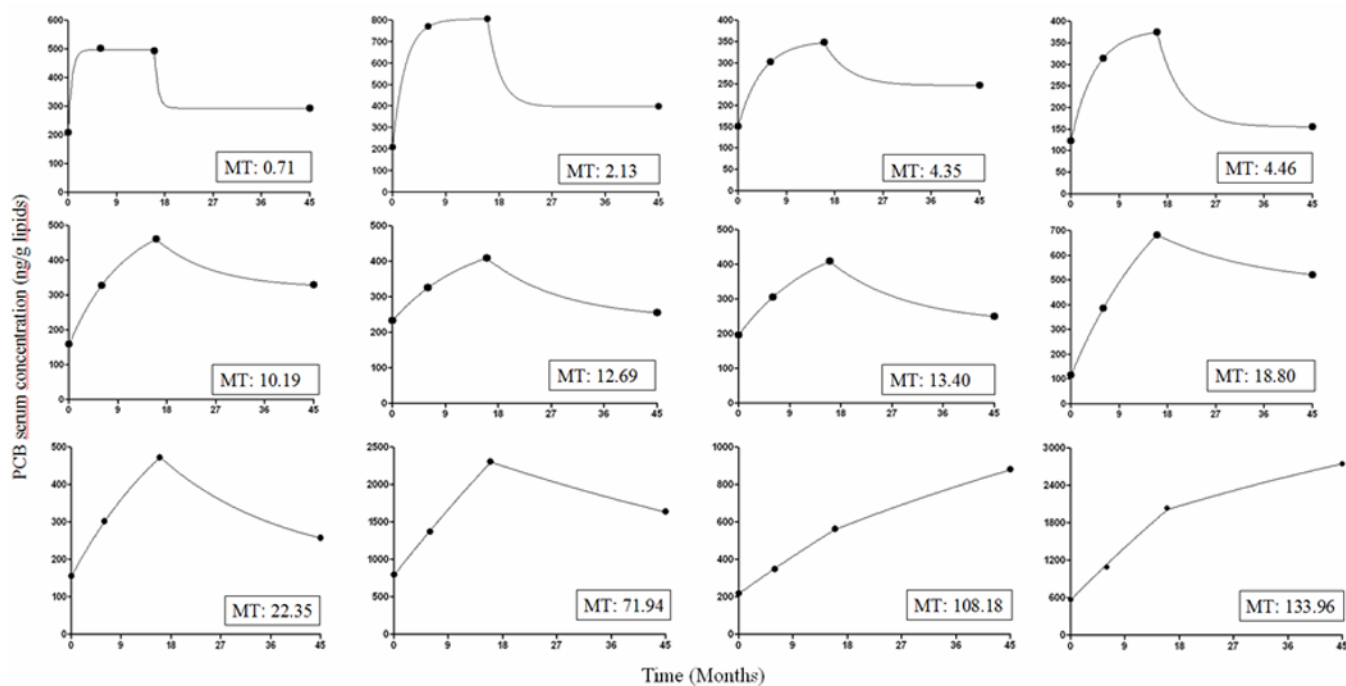
**Figure 4.**
Model approximation of PCB 153 serum concentration values in 12 infants all breast fed 16 months and rank ordered according to increasing mean time (MT) in months.
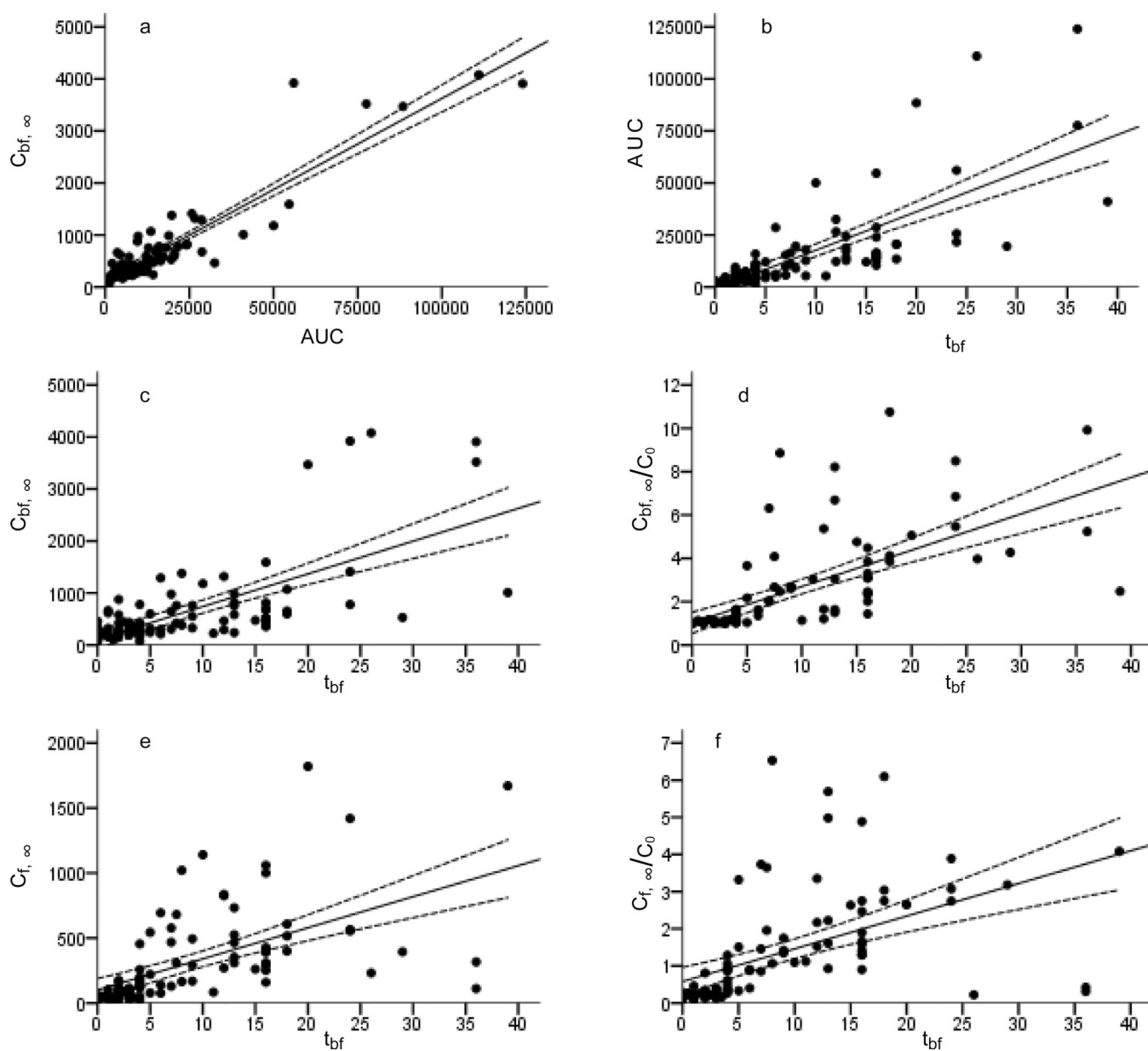
**Figure 5.**
Spearman's correlations between the parameter values AUC vs. $C_{bf, \infty}$ and $t_{bf}$ vs. AUC, $C_{bf, \infty}$, $C_{bf, \infty}/C_0$, $C_{f, \infty}$ and $C_{f, \infty}/C_0$ describing kinetics of PCB 153 serum concentration in 93 infants from birth to month 45 of age.
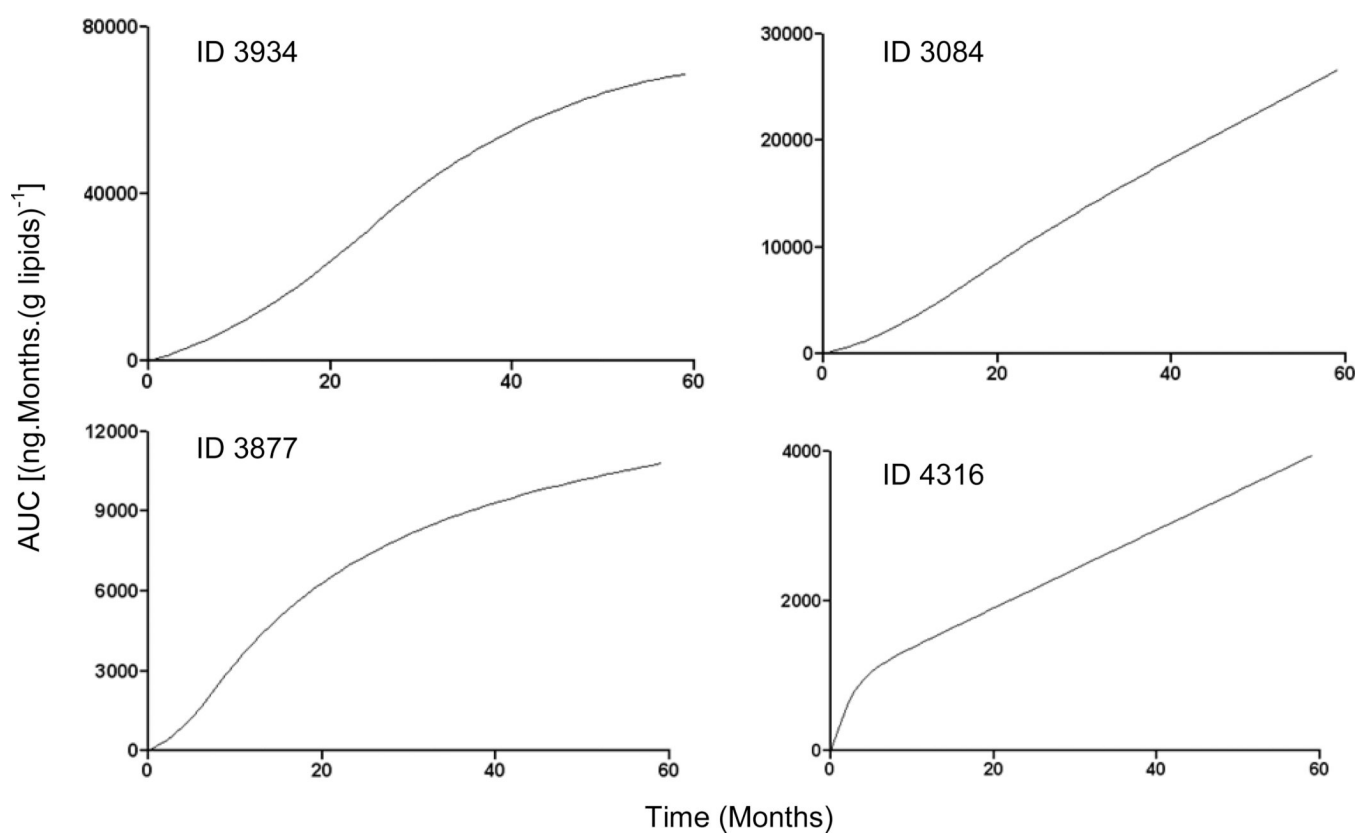
**Figure 6.**
Time dependence of AUC in four children with different duration of breast feeding, $t_{bf}$. For child ID=3934, 3084, 3877 and 4316 $t_{bf}$ was 24, 18, 7, 1 months and $C_{bf, inf}/C_0$ was 11.92, 3.97, 14.4, 1.95, respectively. Note the markedly different vertical scales.

**Table 1**

Descriptive statistics on duration of breast feeding $t_{bf}$ (months) and PCB 153 serum concentration (ng/g lipids) measured in cord blood serum and venous serum at 6, 16 and 45 months of age ($C_0$, $C_6$, $C_{16}$ and $C_{45}$, respectively) (upper part) and on computed parameters MT, AUC, $C_{bf,\infty}$, $C_{f,\infty}$, $C_{bf,\infty}/C_0$, $C_{f,\infty}/C_0$ and $C_{f,\infty}/C_{bf,\infty}$ describing kinetics of PCB 153 serum concentration in 93 infants from birth to month 45 of age (lower part).

| | Mean±SD | Minimum | 5th percentile | 25th percentile | Median | 75th percentile | 95th percentile | Maximum |
|---|---|---|---|---|---|---|---|---|
| $t_{bf}$ | 8.8±8.6 | 0 | 0.4 | 2.8 | 5 | 14 | 26.9 | 39 |
| $C_0$ | 288.8±215.1 | 57.7 | 89.8 | 155 | 209.8 | 359.8 | 808.1 | 1108.4 |
| $C_6$ | 335.7±398.5 | 1.7 | 27.7 | 107.3 | 256.6 | 384.9 | 1253.9 | 2444.9 |
| $C_{16}$ | 401.8±598.9 | 6.1 | 22.5 | 81.2 | 203.1 | 467.1 | 1602.8 | 3503.7 |
| $C_{45}$ | 276.5±349.6 | 16.7 | 28.5 | 74.2 | 156.9 | 326.4 | 1092.8 | 1918.8 |
| MT | 9.3±14.2 | 0.2 | 0.4 | 1.2 | 2.9 | 12 | 45.9 | 75 |
| AUC | 15621.5±21503.8 | 920 | 1515 | 4420 | 9180 | 16850 | 62480 | 124000 |
| $C_{bf,\infty}$ | 669±814 | 70 | 139.1 | 254.2 | 420.2 | 726.6 | 3485 | 4080 |
| $C_{f,\infty}$ | 313.9±358.3 | 14.3 | 25.5 | 75.1 | 168.6 | 440.8 | 1084 | 1820 |
| $C_{bf,\infty}/C_0$ | 2.5±2.2 | 1 | 1 | 1.1 | 1.5 | 3.1 | 8.3 | 10.8 |
| $C_{f,\infty}/C_0$ | 1.4±1.5 | 0.1 | 0.1 | 0.3 | 0.9 | 1.9 | 4.9 | 6.5 |
| $C_{f,\infty}/C_{bf,\infty}$ | 0.5±0.3 | 0.3 | 0.1 | 0.2 | 0.4 | 0.7 | 1.1 | 1.8 |