Chemosphere 85 (2011) 1687–1693

Contents lists available at SciVerse ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

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

Tomáš Trnovec [a,*], Ladislav Dedík [b], Todd A. Jusko [c], Kinga Lancz [a], Ľubica Palkovičová [a], Anton Kočan [a], Eva Šovčíková [a], Soňa Wimmerová [a], Juraj Tihányi [a], Henrieta Patayová [a], Irva Hertz-Picciotto [d]

[a] Slovak Medical University, Limbová 12, 83303 Bratislava, Slovakia
[b] Slovak University of Technology in Bratislava, Faculty of Mechanical Engineering, Vazovova 5, 812 43 Bratislava, Slovakia
[c] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA
[d] Department of Public Health Sciences, University of California, One Shields Avenue, Med Sci 1-C, Davis, CA 95616-8638, USA

ARTICLE INFO

Article history:
Received 11 January 2011
Received in revised form 8 August 2011
Accepted 22 September 2011
Available online 1 November 2011

Keywords:
Polychlorinated biphenyls
Breast feeding
Toxicokinetics
Modeling
Mean residence time
Children

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.

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; Glynn et al., 2008; Hertz-Picciotto et al., 2008; Wilhelm et al., 2008; Lopez-Espinosa et al., 2009; McGlynn et al., 2009; Roze et al., 2009; Terrell et al., 2009; Darnerud et al., 2010), cord blood (Dallaire et al., 2006; Otake et al., 2007; Brucker-Davis et al., 2008; Tan et al., 2009; Sagiv et al., 2010), placental tissue (Reichrtová et al., 1999; Wang et al., 2005; Laisi et al., 2008), breast milk (Heilmann et al., 2006; Glynn et al., 2008; Darnerud et al., 2010), or PCB concentrations measured postnatally in the blood of infants and children (Barr et al., 2006; Sunyer et al., 2008; Darnerud et al., 2010; Grimalt et al., 2010). 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

* Corresponding author. Tel.: +421 2 59370225; fax: +421 2 59370151.
E-mail address: tomas.trnovec@szu.sk (T. Trnovec).

0045-6535/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.chemosphere.2011.09.013

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 two 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 h 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 (Kočan et al., 1994; Čonka et al., 2005). 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 (Fig. 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 $I(t)$ (Fig. 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 ΔC the equation

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

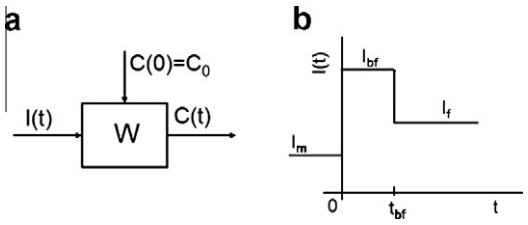

Fig. 1. (a) Definition of system W. I, C is the input respectively the output function of the system. $C(0)$ – Initial condition of system, t – time. (b) Time course of input function $I(t)$, where t is time, I_m, I_{bf} and I_f are hypothetical transfer rates of PCB from mother to fetus, from mother milk to infant and from normal food to infant, respectively. t_{bf} is duration of breast feeding.

where s is Laplace operator and $H(s)$ is transfer function of the system PCB concentration increase of the child ΔC 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

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

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

$$H(s) = \frac{1}{\mathrm{MT}s + 1} \tag{4}$$

With respect to this we cannot estimate 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, $t_{bf} \to \infty$ as

$C_{bf\infty} = C_0 + \Delta C_{bf\infty}$ in time $t \to \infty$

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

$C_{f\infty} = C(0) + \Delta C_f - \Delta C_{bf}$ in time $t \to \infty$

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

$L(t) = \Delta C_{bf\infty}$

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

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

$$\Delta C(t) = \Delta C_{bf\infty}(1 - e^{-\frac{t}{MT}}) \text{ for } t \leq t_{bf} \text{ and} \tag{5}$$

$$\Delta C(t) = \Delta C_{bf\infty}(1 - e^{-\frac{t}{MT}}) + (\Delta C_{bf\infty} - \Delta C_{f\infty})(1 - e^{-\frac{t-t_{bf}}{MT}}) \text{ for } t > t_{bf}. \tag{6}$$

Fig. 2 illustrates Eqs. (1), (5), (6).

Vector λ of estimated model parameters will then be:

$\lambda = (MT, \Delta C_{bf\infty}, \Delta C_{f\infty})$

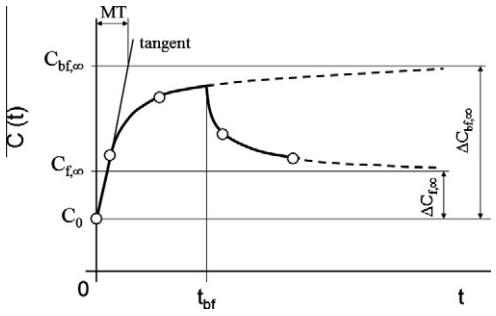

Fig. 2. Illustration of system output function $C(t)$, where t is time, and of the model parameters used for approximation of the concentration of PCB in serum of infants. t_{bf} is duration of breast feeding, $C_{bf,\infty}$ is a hypothetical limit value of PCB concentration increase for t and t_{bf} 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.

The parameters of vector λ 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 Fig. 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.

Fig. 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 two 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 Fig. 5 show that $C_{bf,\infty}$ is related to AUC (Fig. 5a: $r = 0.84$, $p < 0.001$) and that t_{bf} predicts AUC (Fig. 5b: $r = 0.86$, $p < 0.001$), $C_{bf,\infty}$ (Fig. 5c: $r = 0.64$, $p < 0.001$), $C_{bf,\infty}/C_0$ (Fig. 5d: $r = 0.85$, $p < 0.001$), $C_{f,\infty}$ (Fig. 5e: $r = 0.78$, $p < 0.001$) and $C_{f,\infty}/C_0$ (Fig. 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 four 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 four children with largely varying duration of breast feeding (Fig. 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

Table 1
Descriptive statistics on duration of breast feeding t_{bf} (months) and PCB 153 serum concentration (ng g^{-1} 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

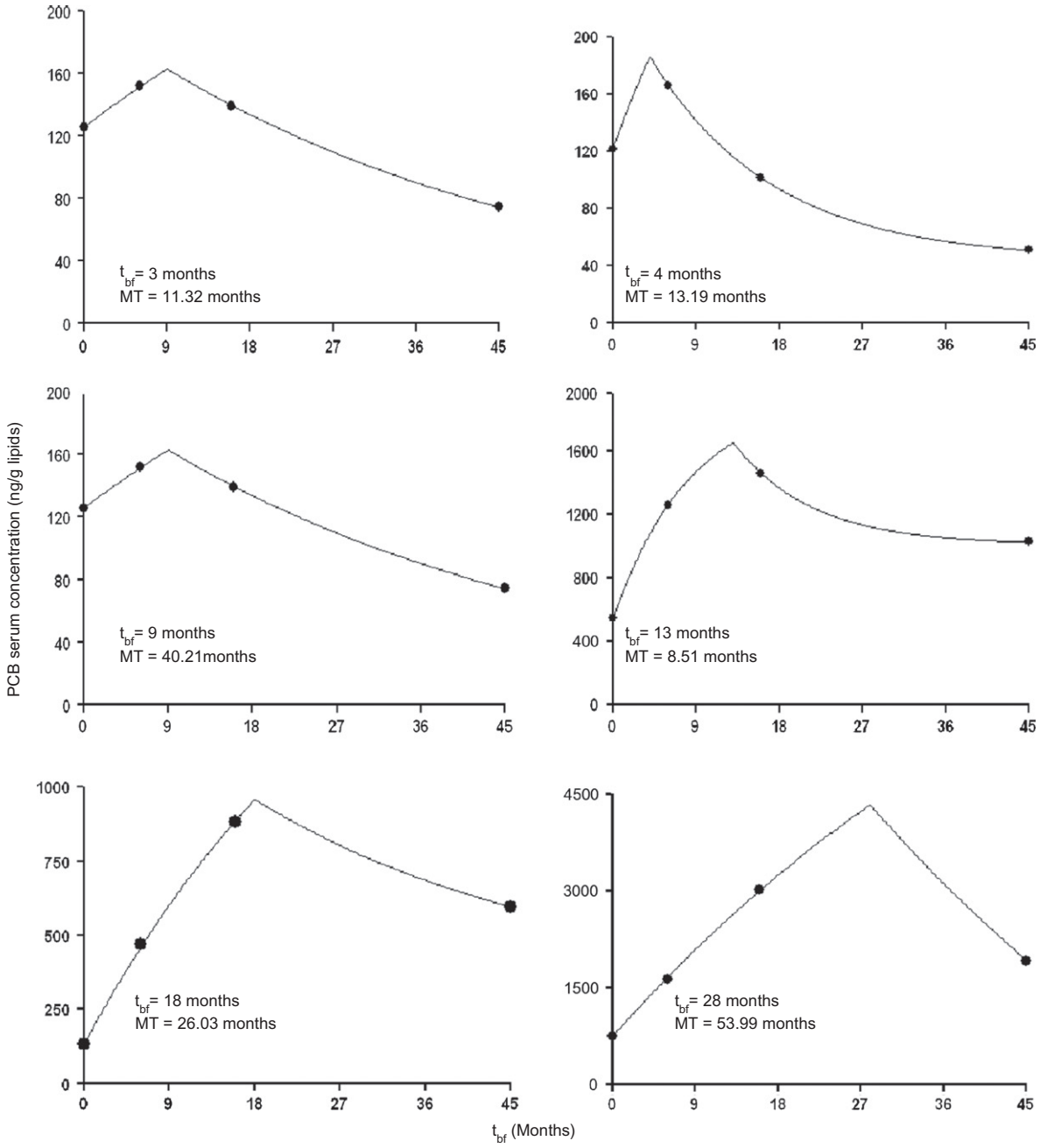

Fig. 3. The measured PCB 153 serum concentrations and the calculated curve for six children with markedly different duration of breast feeding t_{bf}. Note the markedly different vertical scales.

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 (Kreuzer et al., 1997; Patandin et al., 1999; LaKind et al., 2000; Lorber and Phillips, 2002; Kerger et al., 2007).

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

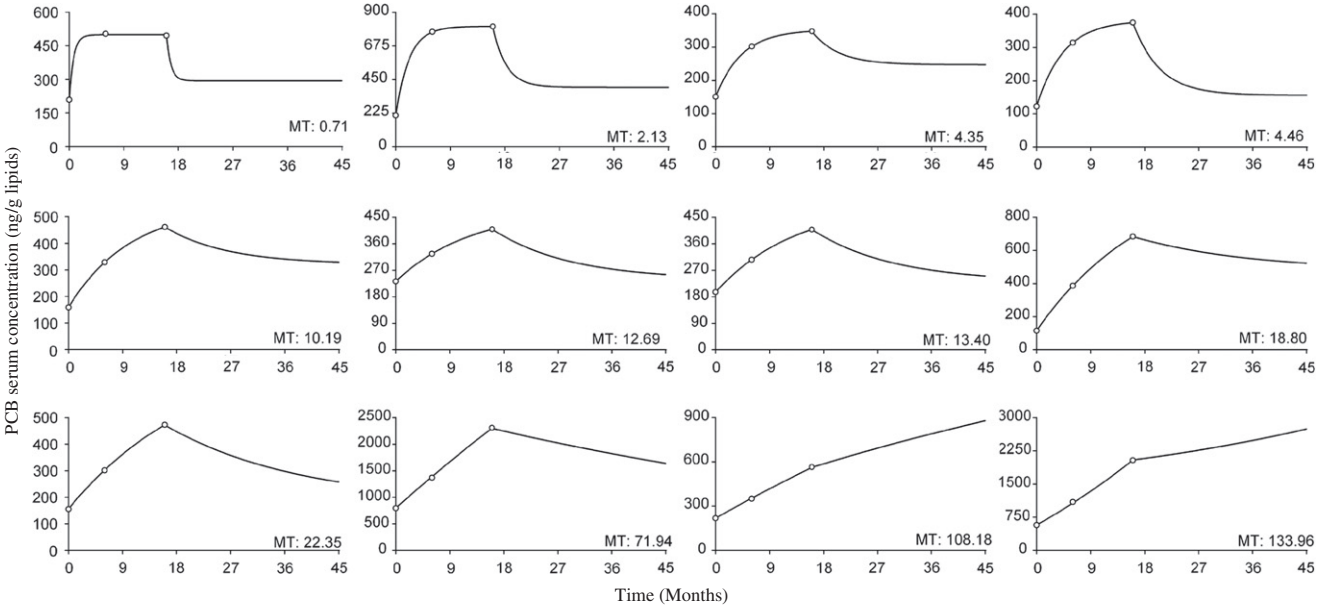

Fig. 4. Model approximation of PCB 153 serum concentration values in 12 infants all breast fed 16 months and rank ordered according to increasing mean time (MT) in months.

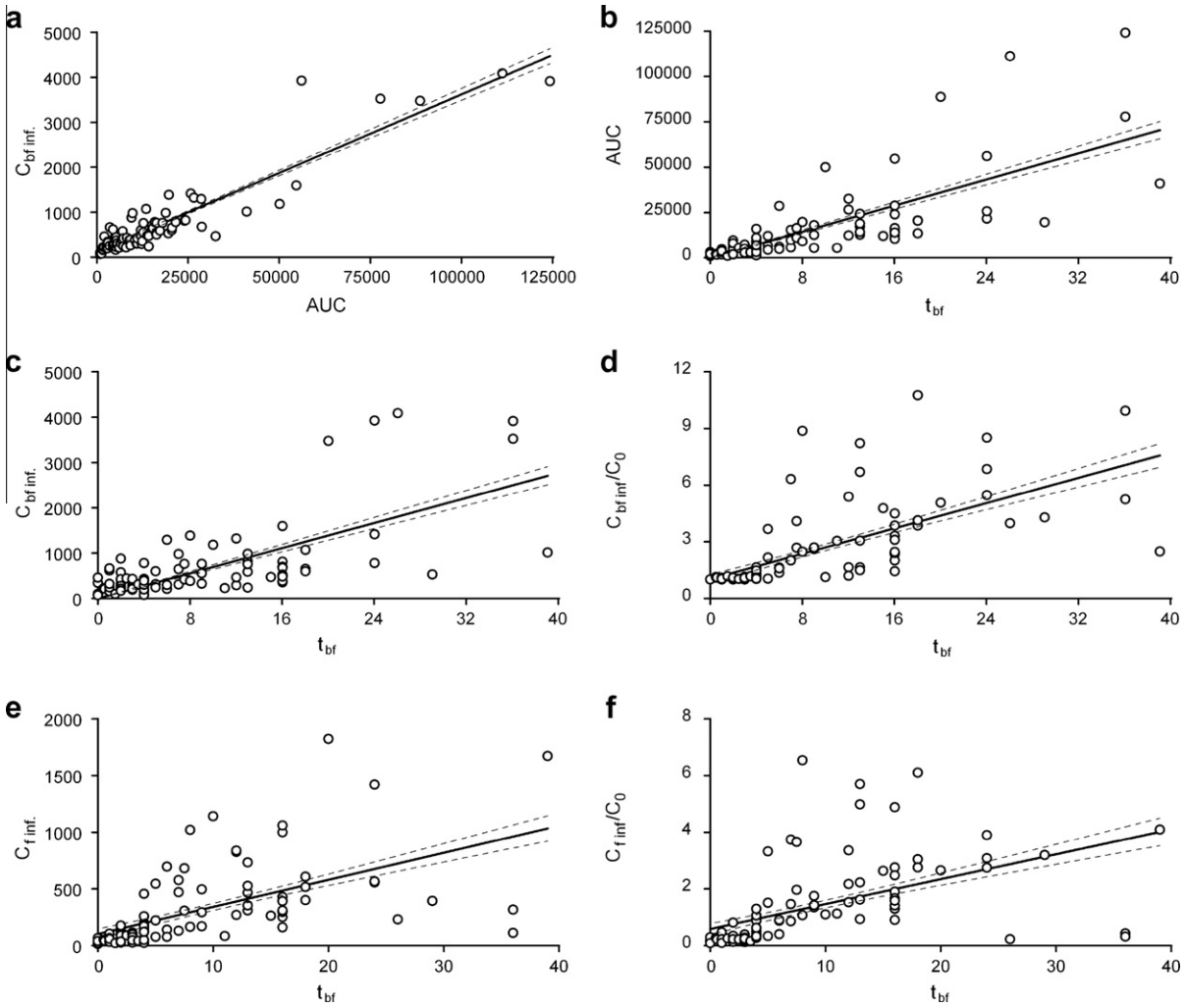

Fig. 5. Spearman's correlations between the parameter values AUC vs. $C_{bf,\infty}$ and t_{bf} vs. AUC, $C_{bf,\infty}$, $C_{bf,\infty}/C_0$, $C_{f,\infty}$ and $C_{f,\infty}/C_0$ describing kinetics of PCB 153 serum concentration in 93 infants from birth to month 45 of age. In figures inf stands for ∞.

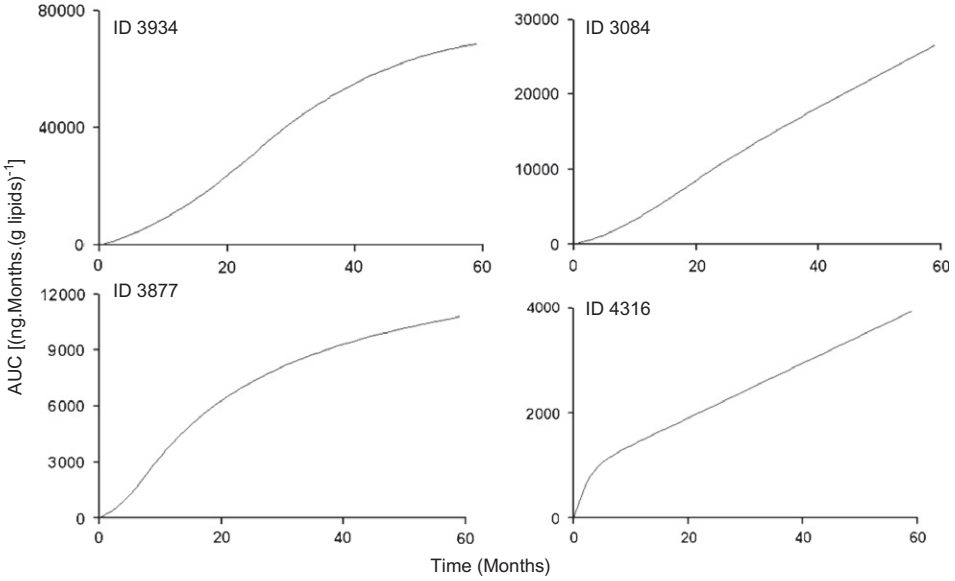

Fig. 6. Time dependence of AUC in four children with different duration of breast feeding, t_{bf}. For child ID = 3934, 3084, 3877 and 4316 t_{bf} was 24, 18, 7, 1 months and $C_{bf,\,inf}/C_0$ was 11.92, 3.97, 14.4, 1.95, respectively. Note the markedly different vertical scales.

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 Fig. 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,b). 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, 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 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.

Acknowledgements

This research received support from National Institutes of Health grant R01-CA096525, from the Slovak Research and Development Agency under the Contract No. LPP-0164-07 and EU Projects INTARESE (No. 018385), HEIMTSA (No. 036913-2), ENVIRISK (No. 044232) and OBELIX (No. 227391) and in part by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences.

References

Akins, J.R., Waldrep, K., Bernert Jr., J.T., 1989. The estimation of total serum lipids by a completely enzymatic 'summation' method. Clin. Chim. Acta. 184, 219–226.
Ayotte, P., Carrier, G., Dewailly, E., 1996. Health risk assessment for Inuit newborns exposed to dioxin-like compounds through breast feeding. Chemosphere 32, 531–542.
Ayotte, P., Muckle, G., Jacobson, J.L., Jacobson, S.W., Dewailly, E., 2003. Assessment of pre- and postnatal exposure to polychlorinated biphenyls: lessons from the Inuit cohort study. Environ. Health Perspect. 111, 1253–1258.
Barr, D.B., Weihe, P., Davis, M.D., Needham, L.L., Grandjean, P., 2006. Serum polychlorinated biphenyl and organochlorine insecticide concentrations in a Faroese birth cohort. Chemosphere 62, 1167–1182.
Brucker-Davis, F., Wagner-Mahler, K., Delattre, I., Ducot, B., Ferrari, P., Bongain, A., Kurzenne, J.Y., Mas, J.C., Fénichel, P., 2008. Cryptorchidism study group from Nice area. Cryptorchidism at birth in Nice area (France) is associated with higher prenatal exposure to PCBs and DDE, as assessed by colostrum concentrations. Hum. Reprod. 23, 708–1718.
Buffham, B.A., Kropholler, H.W., 1973. Tracer kinetics: some general properties, the mean residence time and applications to phase and chemical equilibria. Chem. Eng. Sci. 28, 1081–1089.
Chevrier, J., Eskenazi, B., Holland, N., Bradman, A., Barr, D.B., 2008. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. Am. J. Epidemiol. 168, 298–310.
Čonka, K., Drobná, B., Kočan, A., Petrík, J., 2005. Simple solid-phase extraction method for determination of polychlorinated biphenyls and selected organochlorine pesticides in human serum. J. Chromatogr. A. 1084, 33–38.
Dallaire, F., Dewailly, E., Vézina, C., Muckle, G., Weber, J.P., Bruneau, S., Ayotte, P., 2006. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. Environ. Health Perspect. 114, 1301–1305.
Darnerud, P.O., Lignell, S., Glynn, A., Aune, M., Törnkvist, A., Stridsberg, M., 2010. POP levels in breast milk and maternal serum and thyroid hormone levels in mother-child pairs from Uppsala. Sweden. Environ. Int. 36, 180–187.

Debnath, L., 1995. Integral Transforms and Their Applications. Springer Verlag, Berlin.
Dedík, L., Ďurišová M., 1999. System approach in technical, environmental, and biomedical studies. Publishing House of Slovak University of Technology, Bratislava, ISBN 80-227-1176- 4, 168pp. <http://www.uef.sav.sk/advanced.htm>.
Dedík, L., Ďurišová, M., Ághová, Ľ., 1997. The frequency response method used in modelling environmental systems: a working example. Ecol. Model. 101, 175–184.
Ďurišová, M., Dedík, L., 2005. New mathematical methods in pharmacokinetic modeling. Basic Clin. Pharmacol. Toxicol. 96, 335–342.
Glynn, A., Thuvander, A., Aune, M., Johannisson, A., Darnerud, P.O., Ronquist, G., Cnattingius, S., 2008. Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study. Environ. Health. 7, 62.
Grimalt, J.O., Carrizo, D., Garí, M., Font-Ribera, L., Ribas-Fito, N., Torrent, M., Sunyer, J., 2010. An evaluation of the sexual differences in the accumulation of organochlorine compounds in children at birth and at the age of 4 years. Environ. Res. 110, 244–250.
Heilmann, C., Grandjean, P., Weihe, P., Nielsen, F., Budtz-Jørgensen, E., 2006. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. PLoS. Med. 3, e311.
Hertz-Picciotto, I., Trnovec, T., Kočan, A., Charles, M.J., Čižnár, P., Langer, P., Šovčíková, E., James, R., 2003. PCBs and early childhood development in Slovakia: Study design and background. Fresen. Environ. Bull. 12, 208–214.
Hertz-Picciotto, I., Jusko, T.A., Willman, E.J., Baker, R.J., Keller, J.A., Teplin, S.W., Charles, M.J., 2008. A cohort study of in utero polychlorinated biphenyl (PCB) exposures in relation to secondary sex ratio. Environ. Health. 15, 37.
Hovander, L., Linderholm, L., Athanasiadou, M., Athanassiadis, I., Bignert, A., Fängström, B., Kocan, A., Petrik, J., Trnovec, T., Bergman, A., 2006. Levels of PCBs and their metabolites in the serum of residents of a highly contaminated area in eastern Slovakia. Environ. Sci. Technol. 40, 3696–3703.
Jacobson, J.L., Humphrey, H.E., Jacobson, S.W., Schantz, S.L., Mullin, M.D., Welch, R., 1989. Determinants of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dichlorodiphenyl trichloroethane (DDT) levels in the sera of young children. Am. J. Public Health. 79, 1401–1404.
Karol, M.D., 1990. Mean residence time and the meaning of AUMC/AUC. Biopharm Drug Dispos. 11, 179–181.
Kerger, B.D., Leung, H.W., Scott, P.K., Paustenbach, D.J., 2007. An adaptable internal dose model for risk assessment of dietary and soil dioxin exposures in young children. Toxicol. Sci. 100, 224–237.
Kočan, A., Petrík, J., Drobná, B., Chovancová, J., 1994. Levels of PCBs and some organochlorine pesticides in the human population of selected areas of the Slovak Republic. Chemosphere 29, 2315–2325.
Kreuzer, P.E., Csanády, Gy.A., Baur, C., Kessler, W., Papke, O., Greim, H., Filser, J.G., 1997. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and congeners in infants. A toxicokinetic model of human lifetime body burden by TCDD with special emphasis on its uptake by nutrition. Arch. Toxicol. 71, 383–400.
Laisi, S., Kiviranta, H., Lukinmaa, P.L., Vartiainen, T., Alaluusua, S., 2008. Molar-incisor-hypomineralisation and dioxins: new findings. Eur. Arch. Paediatr. Dent. 9 (4), 224–227.
LaKind, J.S., Berlin, C.M., Park, C.N., Naiman, D.Q., Gudka, N.J., 2000. Methodology for characterizing distributions of incremental body burdens of 2,3,7,8-TCDD and DDE from breast milk in North American nursing infants. J. Toxicol. Environ. Health Part A. 59, 605–639.
LaKind, J.S., Berlin, C.M., Sjödin, A., Turner, W., Wang, R.Y., Needham, L.L., Paul, I.M., Stokes, J.L., Naiman, D.Q., Patterson Jr., D.G., 2009. Do human milk concentrations of persistent organic chemicals really decline during lactation? Chemical concentrations during lactation and milk/serum partitioning. Environ. Health Perspect. 117, 1625–1631.
Lanting, C.I., Fidler, V., Huisman, M., Boersma, E.R., 1998. Determinants of polychlorinated biphenyl levels in plasma from 42-month-old children. Arch. Environ. Contam. Toxicol. 35, 135–139.
Linderholm, L., Park, J.S., Kocan, A., Trnovec, T., Athanasiadou, M., Bergman, K., Hertz-Picciotto, I., 2007. Maternal and cord serum exposure to PCB and DDE methyl sulfone metabolites in eastern Slovakia. Chemosphere 69, 403–410.
Longnecker, M.P., Wolff, M.S., Gladen, B.C., Brock, J.W., Grandjean, P., Jacobson, J.L., Korrick, S.A., Rogan, W.J., Weisglas-Kuperus, N., Hertz-Picciotto, I., Ayotte, P., Stewart, P., Winneke, G., Charles, M.J., Jacobson, S.W., Dewailly, E., Boersma, E.R., Altshul, L.M., Heinzow, B., Pagano, J.J., Jensen, A.A., 2003. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ. Health Perspect. 111, 65–70.
Lopez-Espinosa, M.J., Vizcaino, E., Murcia, M., Llop, S., Espada, M., Seco, V., Marco, A., Rebagliato, M., Grimalt, J.O., Ballester, F., 2009. Association between thyroid hormone levels and 4,4′-DDE concentrations in pregnant women (Valencia, Spain). Environ. Res. 109, 479–485.
Lorber, M., Phillips, L., 2002. Infant Exposure to Dioxin-like Compounds in Breast Milk. Environ. Health Perspect 110, A 325–A 332.
McGlynn, K.A., Guo, X., Graubard, B.I., Brock, J.W., Klebanoff, M.A., Longnecker, M.P., 2009. Maternal pregnancy levels of polychlorinated biphenyls and risk of hypospadias and cryptorchidism in male offspring. Environ. Health Perspect. 117, 1472–1476.
Milbrath, M.O., Wenger, Y., Chang, C.W., Emond, C., Garabrant, D., Gillespie, B.W., Jolliet, O., 2009. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ. Health Perspect. 117, 417–425.
Otake, T., Yoshinaga, J., Enomoto, T., Matsuda, M., Wakimoto, T., Ikegami, M., Suzuki, E., Naruse, H., Yamanaka, T., Shibuya, N., Yasumizu, T., Kato, N., 2007. Thyroid hormone status of newborns in relation to in utero exposure to PCBs and hydroxylated PCB metabolites. Environ. Res. 105, 240–246.
Park, J.S., Bergman, A., Linderholm, L., Athanasiadou, M., Kocan, A., Petrik, J., Drobna, B., Trnovec, T., Charles, M.J., Hertz-Picciotto, I., 2008. Placental transfer of polychlorinated biphenyls, their hydroxylated metabolites and penta chlorophenol in pregnant women from eastern Slovakia. Chemosphere 70, 1676–1684.
Park, J.S., Linderholm, L., Charles, M.J., Athanasiadou, M., Petrik, J., Kocan, A., Drobna, B., Trnovec, T., Bergman, A., Hertz-Picciotto, I., 2007. Polychlorinated biphenyls and their hydroxylated metabolites (OH-PCBS) in pregnant women from eastern Slovakia. Environ. Health Perspect. 115, 20–27.
Patandin, S., Dagnelie, P.C., Mulder, P.G., Op de Coul, E., van der Veen, J.E., Weisglas-Kuperus, N., Sauer, P.J., 1999. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: a comparison between breast-feeding, toddler, and longterm exposure. Environ. Health Perspect. 107, 45–51.
Patandin, S., Weisglas-Kuperus, N., de Ridder, M.A., Koopman-Esseboom, C., van Staveren, W.A., van der Paauw, C.G., Sauer, P.J., 1997. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy. Am. J. Public Health. 87, 1711–1714.
Reichrtová, E., Ciznár, P., Prachar, V., Palkovicová, L., Veningerová, M., 1999. Cord serum immunoglobulin E related to the environmental contamination of human placentas with organochlorine compounds. Environ. Health Perspect. 107, 895–899.
Roze, E., Meijer, L., Bakker, A., Van Braeckel, K.N., Sauer, P.J., Bos, A.F., 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ. Health Perspect. 117, 1953–1958.
Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., Korrick, S.A., 2010. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. Am. J. Epidemiol. 171, 593–601.
Sonneborn, D., Park, H.Y., Babinska, K., Nguyen, D.V., Palkovicova, L., Trnovec, T., Kocan, A., Hertz-Picciotto, I., 2008a. Association of PCB exposure to food-specific consumption and sources in Eastern Slovakia. J. Expo. Anal. Environ. Epidemiol. 18, 86–87.
Sonneborn, D., Park, H.Y., Petrik, J., Kocan, A., Palkovicova, L., Trnovec, T., Nguyen, D., Hertz-Picciotto, I., 2008b. Prenatal polychlorinated biphenyl exposures in eastern Slovakia modify effects of social factors on birthweight. Paediatr. Perinat. Epidemiol. 22, 202–213.
Sunyer, J., Alvarez-Pedrerol, M., To-Figueras, J., Ribas-Fitó, N., Grimalt, J.O., Herrero, C., 2008. Urinary porphyrin excretion in children is associated with exposure to organochlorine compounds. Environ. Health Perspect. 116, 1407–1410.
Tan, J., Loganath, A., Chong, Y.S., Obbard, J.P., 2009. Exposure to persistent organic pollutants in utero and related maternal characteristics on birth outcomes: a multivariate data analysis approach. Chemosphere 74, 428–433.
Terrell, M.L., Berzen, A.K., Small, C.M., Cameron, L.L., Wirth, J.J., Marcus, M., 2009. A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB). Environ. Health. 8, 35.
Veng-Pedersen, P., 1989a. Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (Part I). Clin Pharmacokinet. 17, 345–366.
Veng-Pedersen, P., 1989b. Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (Part II). Clin Pharmacokinet. 17, 424–440.
Verner, M.A., Ayotte, P., Muckle, G., Charbonneau, M., Haddad, S., 2009. A physiologically based pharmacokinetic model for the assessment of infant exposure to persistent organic pollutants in epidemiologic studies. Environ. Health Perspect. 117, 481–487.
Verner, M.A., Plusquellec, P., Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W., Jacobson, J.L., Charbonneau, M., Haddad, S., 2010. Alteration of infant attention and activity by polychlorinated biphenyls: unravelling critical windows of susceptibility using physiologically based pharmacokinetic modeling. Neurotoxicology 31, 424–431.
Wang, S.L., Su, P.H., Jong, S.B., Guo, Y.L., Chou, W.L., Päpke, O., 2005. In utero exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ. Health Perspect. 113, 1645–1650.
Wilhelm, M., Wittsiepe, J., Lemm, F., Ranft, U., Krämer, U., Fürst, P., Röseler, S.C., Greshake, M., Imöhl, M., Eberwein, G., Rauchfuss, K., Kraft, M., Winneke, G., 2008. The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat. Res. 659, 83–92.
Yamaoka, K., Nakagawa, T., Uno, T., 1978. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetics equations. J. Pharmacokinet. Biopharm. 6, 165–175.
Young, J., Schwetz, B., Willhite, C., Kacew, S., 1996. Symposium on pharmacokinetics/pharmacodynamics in the developing system and impact on risk assessment: executive summary. J. Toxicol. Environ. Health 49, 339–355.