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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.

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

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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

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

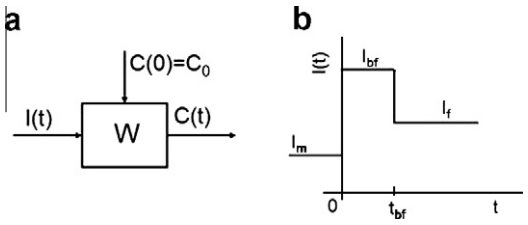

Fig. 1. (a) Definition of system W. I, C is the input respectively the output function of the system. $C(0)$ – Initial condition of system, t – time. (b) Time course of input function $I(t)$, where t is time, I_m, I_{bf} and I_f are hypothetical transfer rates of PCB from mother to fetus, from mother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

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