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Application of a pharmacokinetic model in characterizing sources of polychlorinated biphenyl exposure and determining threshold daily intakes for adverse health effects in infants and toddlers

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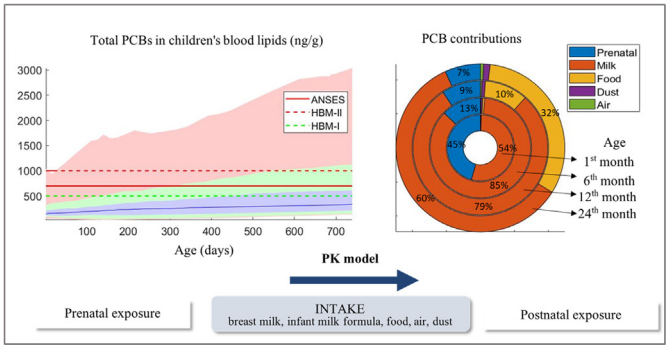
HIGHLIGHTS

- We estimated the new threshold daily intakes (TEDI) of PCBs for breastfed children.
- TEDI reflect threshold PCB concentrations in blood for adverse health effects.
- The contribution of exposure PCB sources for infants and toddler was calculated.

GRAPHICAL ABSTRACT



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ABSTRACT

Characterization of PCB exposure sources for vulnerable population groups is essential to minimize the health effects of PCB exposure. At the same time, it is important to consolidate the knowledge on threshold intakes of PCBs for infants and toddlers to prevent health effects. We estimated total PCB concentrations from birth to 2 years of age in children from Slovak and Czech populations, which continue to have high PCB concentrations in breast milk. Using a pharmacokinetic (PK) model, we characterized dominant PCB exposure sources and estimated new threshold estimated daily intakes (TEDI) (above which adverse effects cannot be excluded) for postnatal PCB exposure in infants and toddlers. In the PK model, concentrations of seven indicator PCBs in breast milk and cord blood samples from 291 mother-child pairs from the Slovak birth cohort, and 396 breast milk samples from Czech mothers we used, together with their physiological characteristics and PCB concentrations from other exposure sources (food, dust, air). The estimated total PCB concentrations in children's blood at different ages were compared with threshold PCB concentrations of 500, 700 and 1000 $ng \cdot g_{lipid}^{-1}$ in serum proposed by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) and the German Environment Agency (UBA), above which possible adverse health effects may be expected. We estimated that up to 20.6% of Slovak children and up to 45.7% of Czech children at two years of age exceeded the

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Safety standards
Infant exposure

threshold value of 700 ng·g_{lipid}^{-1} in blood. Mean TEDIs leading to values of 500 ng·g_{lipid}^{-1} in blood for children up to two years ranged between 110 and 220 ng·kg^{-1}·bw·day^{-1}, varying according to breastfeeding duration. Breast milk and prenatal exposure contributed to 71%–85% of PCBs exposure at two years of age. In contrast, the contributions of PCBs from dust and indoor air were negligible.

1. Introduction

Polychlorinated biphenyl (PCB) exposure of human populations is widespread as these chemicals have been measured and detected in human tissues, including maternal blood, cord blood, and breast milk of populations around the globe (Faroon and Ruiz, 2016; Undeman et al., 2018). Measured PCB concentrations in these matrices can be used to estimate prenatal and postnatal exposure of infants and toddlers, which can be compared to threshold values above which toxic (in this case, neurotoxic and immunotoxic) effects cannot be excluded. PCB exposure of children in the early years is an important health issue since it has been shown that PCB breast milk concentrations in many countries exceed safety standards by up to two orders of magnitude, with the highest reported concentrations in the Czech and Slovak Republics (van den Berg et al., 2017).

Breast milk was found to be the main PCB exposure source for breastfed infants up to six months (Ayotte et al., 2003; Patandin et al., 1999) and for toddlers up to 45 months (Caspersen et al., 2016; Garí et al., 2019; Jacobson et al., 1989; Lancz et al., 2015; Trnovec et al., 2011; Verner et al., 2013). The duration of breastfeeding was also a major determinant of elevated levels of higher-chlorinated PCBs in school-age children (7–10 years) (Barr et al., 2006; Karmaus et al., 2001), and breastfeeding for six months contributed about 12–14% to the cumulative PCB/dioxin toxic equivalents (TEQ) intake at 25 years of age (Patandin et al., 1999). Prenatal and postnatal PCB exposure is associated with adverse effects on neurodevelopment, growth, behavior, and sexual and pubertal development of children (Berghuis and Roze, 2019; Iszatt et al., 2015; Ribas-Fitó et al., 2001; Rosenquist et al., 2017).

Estimated daily PCB intake from breast milk is generally used for evaluating postnatal PCB exposure. The standard way to evaluate children's PCB total intake or estimated daily intake (EDI) during breastfeeding is by multiplying the lipid-adjusted content of PCBs in breast milk by the lipid concentration in breast milk and by the daily volume of breast milk consumed. EDIs are compared with safety standards for oral exposure such as a tolerable daily intake of 10 ng·kg^{-1}·bw day^{-1} for the sum of indicator PCBs (iPCBs) (RIVM) (Baars et al., 2001), the minimum risk level (MRL) 30 ng·kg^{-1}·bw day^{-1} for all PCBs for intermediate-duration oral exposure (15–364 days) and 20 ng·kg^{-1}·bw day^{-1} for chronic oral exposure (ASTDR, 2000). However, this approach has some limitations. Exposure based solely on PCB levels in breast milk and duration of breastfeeding may lead to exposure misclassification (Verner et al., 2013) because assuming a constant postnatal exposure does not reflect physiological changes in mother and child. Additionally, estimated daily intakes of breastfed infants and toddlers can easily exceed safety standards because safety standards are generally set for chronic or subchronic exposure and do not take into account the high PCB intake during breastfeeding. As a result, it is difficult to assess how much risk the exceedance of safety standards poses for early childhood development. Moreover, threshold intakes for infants and toddlers, which can lead to possible health effects, are still missing.

Another way to assess the risk of PCB exposure to children is to compare PCB concentrations in children's blood to threshold values above which possible adverse health effects may be expected. For total PCBs, a threshold value of 700 ng·g_{lipid}^{-1} in pregnant women, women of childbearing age, breastfeeding women, and children under three years of age was proposed by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), based on an evaluation of critical effects on the mental and motor development in children exposed to PCBs in utero (ANSES, 2010). The German Environment Agency (UBA, 2012) proposed human biomonitoring values HBM-I (below which no adverse health effect is expected) and HBM-II (above which adverse health effects are possible) for PCBs, considering critical endpoints, including neurotoxic and immunotoxic effects. Specifically, for total PCBs in infants, toddlers, and women of childbearing age, HBM-I and HBM-II values in serum of 3500 ng·l^{-1} serum (i.e. 500 ng·g_{lipid}^{-1} in serum) and 7000 ng·l^{-1} serum (i.e. 1000 ng·g_{lipid}^{-1} in serum), respectively, were proposed. To compare with blood threshold values, ideally concentrations in children's blood should be measured over a longer period, which is, however, difficult due to ethical considerations of repeatedly taking children's blood. An alternative is to estimate PCB concentrations in children's blood using a model approach, e.g. using a pharmacokinetic model, based on PCB concentrations measured in mother's milk or maternal and cord blood (Stigum et al., 2015; Verner et al., 2013; Verner et al., 2009), a "system model" (Trnovec et al., 2011), or a regression model (Lancz et al., 2015) based on time-series serum concentration measurements and duration of breastfeeding.

In this study, by using a pharmacokinetic (PK) model, we calculated the total PCB concentration from birth to 24 months in children's blood and estimated the threshold intakes *TEDIs* that lead to established critical PCB concentrations in blood. PCB concentrations in cord blood and breast milk from 291 mother-child pairs from the Slovak population and 396 breast milk samples from the Czech population were used to set up the PK model. The main exposure sources to PCB in infants and toddlers up to two years of age were also identified. To our knowledge, our *TEDIs* are the first threshold daily intake values for breastfed infants and toddlers during the first two years of life, estimated by taking into account the main exposure sources and child growth; they reflect PCB concentrations in blood above which adverse health effects cannot be excluded.

2. Material and methods

2.1. Biomonitoring studies

In the project "Prospective cohort study of developmental origins of adult diseases in the Slovak population" (PRENATAL; 2008–2013), cord blood and breast milk samples (within the 6th week after delivery) from 291 mothers living in eight Slovak regions were collected between 2010 and 2013. Mothers were recruited at the 10th week of pregnancy at the gynaecological clinics based on their signed informed consent and followed until delivery and afterwards up to 18 months of age of their child. In both cord blood and breast milk samples, the concentrations of 7 iPCBs (28, 52, 101, 118, 138, 153, and 180) were measured (Čonka et al., 2005; Drobná et al., 2011). In cord blood, the total lipid concentrations were estimated using the enzymatic summation method (Akins et al., 1989), and PCB concentrations were expressed as ng PCB/g lipids. Similarly, PCB concentrations in breast milk were standardized to lipid content. The concentrations of PCBs in cord blood and breast milk and the total number of samples for individual PCBs are presented in the Supplementary Material (SM), Table SM1. The project PRENATAL was approved by the Ethical Committee of the Slovak Medical University in June 30, 2009.

In the Czech human cross-sectional biomonitoring study (CZ-HBM) (Černá et al., 2017), conducted since 1996, PCBs were measured in breast milk samples collected between 2 and 8 weeks after birth. From this dataset, we selected a subset (396 mothers) from the period between 2009 and 2011, which is coeval to the PRENATAL cohort sampling period. A detailed description of the breast milk sampling and analysis procedures, and population characteristics of CZ-HBM has been provided elsewhere (Banyiova et al., 2017; Černá et al., 2007; Mikeš et al., 2012). The concentrations of PCBs in breast milk and the total number of samples for individual PCBs from CZ-HBM data included in this study are presented in Table SM1.

Both the CZ-HBM and PRENATAL studies collected additional information on child gender, pre-pregnancy weight and body mass index (BMI) of the mothers, and the mothers' age and parity. In contrast, information about mothers' weight and BMI at the end of pregnancy and childbirth weight and breastfeeding weeks was available only for the PRENATAL cohort. For these characteristics of mothers and children, descriptive statistics are presented in Table 1.

2.2. Model description and parametrization

The PK model simulates exposure to PCBs in children including lactation transfer from the mother to the infant and/or intakes from infant milk formulas, food, indoor air and dust. The PCB exposure through breast milk is based on a modified version of the pharmacokinetic model proposed by Stigum et al., 2015. This model includes: 1) a mass-balance equation for PCBs in the mother (used to estimate the total PCB mass in the mother's body and PCB concentration in breast milk at a time), 2) a mother-to-child PCB transfer equation via lactation, and 3) a mass-balance equation for the child (used to estimate total PCB mass in a child's body at a time). Moreover, equations for iPCB intake from infant's formula, food, indoor air and dust, and the elimination rate constant of iPCBs were added to the PK model. Equations and a detailed description of the pharmacokinetic model are provided in the SM.

2.2.1. PCB concentration in cord blood and breast milk

The initial iPCB concentration in the child's blood (C_{child} at time t_0) was set as the measured iPCB concentration in cord blood at birth. The initial iPCB concentration in the breast milk (C_{milk} at time t_0) at the time of birth was set as the measured concentrations in breast milk collected up to 6 weeks after birth in the PRENATAL cohort and between 2 and 8 weeks in CZ-HBM. To estimate iPCB concentrations in cord blood for Czech children (concentrations in cord blood were not measured in CZ-HBM), we computed regression equations between iPCB concentrations in cord blood ($ng \cdot g_{lipid}^{-1}$) and breast milk ($ng \cdot g_{lipid}^{-1}$) from the PRENATAL data (Table SM2); for a detailed description see SM.

The proportion of nursing was taken from questionnaires of the PRENATAL cohort and different scenarios of breastfeeding duration for both the PRENATAL cohort and CZ-HBM (see Section 2.3.1). The proportion of nursing for partially breastfed or non-breastfed children, the proportion of infant milk formula, and of complementary foods per age (in months) from WHO (WHO, 2006) was added to the PK model (Table SM3).

2.2.2. Physiological parameters

The birth weights and gender were taken from the PRENATAL cohort and the CZ-HBM. The percentage increase in weight for each day (from birth up to two years) was calculated from standard WHO growth curves separately for boys and girls, and individual body weight profiles BW_{child} (from birth up to two years) were generated for each child. The amount of total lipids in the child, Fat_{child} (g), was calculated as a fraction of fat in the child's body from the total body weight at a given age. The fraction of lipids from bodyweight BW for boys and girls was used for different ages (Butte et al., 2000). The amount of fat in mothers, Fat_{mother} (g), was calculated based on the fraction of mother's body fat by using the mother's age, weights and BMI (Deurenberg et al., 1991). As the mothers' weight was not measured after delivery, we assumed that the weight six months after delivery was 2 kg above pre-pregnancy weight (Butte et al., 2003).

2.2.3. Food, indoor air, and dust

The average concentrations of iPCBs in indoor air and dust measured in samples collected from 20 homes in Brno (Czech Republic) in 2013 (Audy et al., 2018) (Table SM4) and 60 homes in Eastern Slovakia in 2015 (Demirtepe et al., 2019) were taken as input parameters in our pharmacokinetic model to calculate iPCB intakes from dust and air. The average PCB intakes from food from local markets for mothers and children between 2009 and 2012 were taken from the Environmental Health Monitoring System in the Czech Republic (NIPH, 2015) (Table SM4). The intakes of iPCBs through food were calculated by combining measured iPCB concentrations in food and dietary recommendations based on age and gender (NIPH, 2015). The median iPCB concentration of 1.15 $ng \cdot g_{lipid}^{-1}$ in infant formula was estimated from the most frequently used infant milk formulas available in Slovakia (Drobná et al., 2011). Other parameters used for intake calculation were absorption factors of PCBs for dust, air, and food (U.S. EPA, 2012). Recommended values for the different age categories of children were used for the ingestion rate of dust, the inhalation rate, and the time spent indoors (U.S. EPA, 2011) (Table SM4).

2.2.4. PCB elimination

Elimination due to biotransformation and fecal excretion was based on half-lives ($t_{1/2}$, days) derived from cross-sectional data for all iPCB (Ritter et al., 2011) except PCB 101, where the half-life was taken from (Schettgen et al., 2012) (Table SM5). Elimination was not included in the original PK model proposed by Stigum et al. (2015) because the model was used for higher-chlorinated PCBs with a long half-life and the elimination of these substances for infants and toddlers is negligible. In our model, however, we also model the concentration of lower-chlorinated PCBs (28, 52 and 101), with a shorter half-life, and elimination is relevant.

2.3. Risk assessment of PCB exposure

2.3.1. PCB exposure scenarios

The PK model developed in this study simulates the individual prenatal and postnatal PCB exposure of a child. According to each child's body weight, breastfeeding duration, and child-mother concentrations of iPCBs in cord blood and breast milk, as well as iPCB concentrations in food, infant

Table 1
Characteristics of mothers and children.

		PRENATAL (n = 291)			CZ-HBM (n = 396)		
		Median	10^{th}–90^{th}	Min–Max	Median	10^{th}–90^{th}	Min–Max
Age (years)		29	23–35	17–44	29	24–34	17–38
Pre-pregnancy mother's weight (kg)		61	51–80	42–115	68	57–83	45–123
Mother's weight (kg) at end of pregnancy		76.75	64–95	54–130		NA	
BMI ($kg \cdot m^{-2}$) pre-pregnancy		22.1	19.1–29	15.6–41.7	24.2	20.7–29.8	16.7–38.4
BMI ($kg \cdot m^{-2}$) at end of pregnancy		27.7	23.7–33.9	20–47.8		NA	
Child's birth weight (g)		3370	2800–3920	1850–4750		NA	
Breastfeeding (weeks)	Breastfed	36	4–96	0–148		NA	
	Exclusively breastfed	20	2–26	0–116		NA	
Gender	Female		229; 46.2%			194; 49%	
	Male		267; 53.8%			202; 51%	
Maternal parity	First child		209; 44.9%			396; 100%	
	Second child		192; 41.3%			0	
	Third child or more		64; 13.8%			0	

For continuous variables, the median, 10^{th}–90^{th} percentiles, and minimum and maximum are shown; for categorical variables, the counts and percentages are shown; NA means not available.

milk formula, and indoor dust and air, the individual PCB profiles from birth to 24 months of age for the Czech and Slovak populations (697 = 291 + 396 children) were calculated. The total PCB concentration was calculated as the concentration of all iPCBs multiplied by two because the sum of indicator congeners is approximately 50% of the total PCB concentration (Kraft et al., 2017).

Four different exposure scenarios with different breastfeeding durations were considered to describe the possible exposure of infants and toddlers to PCBs and to estimate the influence of breastfeeding duration on children's exposure. These scenarios included: i) self-reported breastfeeding duration for each mother participating in the PRENATAL cohort; ii) median breastfeeding estimated from the PRENATAL cohort (5 months of exclusive breastfeeding, four months partial); iii) long breastfeeding, where the 90th percentile of breastfeeding weeks from the PRENATAL cohort was used (6.5 months of exclusive breastfeeding, 17.5 months partial), and iv) short breastfeeding, where the 10th percentile of breastfeeding weeks from the PRENATAL cohort was used (2 weeks of exclusive breastfeeding, two weeks partial) (Table 1).

The total modelled PCB concentrations in blood lipids was calculated for each child and exposure scenario and compared with threshold values for PCBs in blood: the ANSES critical value (CV) (ANSES, 2010) and HBM-I, II (UBA, 2012) (see Section 2.3.2).

2.3.2. Threshold estimated daily intake

First, estimated daily intakes (EDIs) of the sum of 7 iPCBs were calculated for each child based on changes in the child's body weight (adipose tissue) with age, the proportion of various food items (breast milk, infant milk formula, and complementary food) specified for each day and change of lipids in breast milk during the breastfeeding period (see I_{total}, Eq. (7) in SM). EDIs were compared with the tolerable daily intake (oral exposure) of 10 $ng{\cdot}kg^{-1}{\cdot}bw{\cdot}day^{-1}$ for the sum of iPCBs (RIVM) (Baars et al., 2001), the minimum risk level (MRL) of 30 $ng{\cdot}kg^{-1}{\cdot}bw{\cdot}day^{-1}$ for total PCBs for intermediate-duration oral exposure (15–364 days) (ASTDR, 2000), and the tolerable daily intake (TDI) of 400 $ng{\cdot}kg^{-1}{\cdot}bw{\cdot}day^{-1}$ accepted in the Czech Republic for children (Ruprich et al., 2011). Percentages of children above those safety standards for each exposure scenario were calculated.

We developed the new concept of "threshold estimated daily intakes" (TEDIs) of iPCBs that correspond to the threshold concentrations of total PCBs in children's blood: the ANSES CV (700 $ng{\cdot}g^{-1}$ blood lipids) for pregnant women, women of childbearing age, breastfeeding women, and children under three years of age, based on evaluation of critical effects on the mental and motor development in children exposed to PCBs in utero (ANSES, 2010) and the threshold values of total PCBs in blood proposed by UBA for infants, toddlers, and women of childbearing age based on critical endpoints, including neurotoxic and immunotoxic effects: HBM-I (500 $ng{\cdot}g^{-1}$ blood lipids), below which no adverse health effect is expected, and HBM-II (1000 $ng{\cdot}g^{-1}$ blood lipids), above which adverse health effects are possible (UBA, 2012).

We calculated two types of *TEDI* values, depending on the age at which the blood threshold values (CV, HBM-I, HBM-II) are reached: i) $TEDI_{low}$ (CV, HBM-I, HBM-II) are the temporal averages of time series of estimated daily iPCB intakes from birth up to two years for 3, 6, 9, 12, 18 and 24 months of breastfeeding that reach the thresholds values CV, HBM-I and HBM-II of total PCBs concentrations in blood at the age two years; ii) $TEDI_{high}$ (CV, HBM-I, HBM-II) are the temporal averages of time series of estimated daily iPCB intakes for 3, 6, 9, 12, 18 and 24 months of breastfeeding that lead to the critical blood concentrations (CV, HBM-I and HBM-II) of total PCB at the end of breastfeeding.

Both $TEDI_{low}$ and $TEDI_{high}$ refer to the breastfeeding period. $TEDI_{low}$ should not be exceeded in order to avoid exceeding the threshold values (HBM-I, HBM-II and CV) at two years of age, while $TEDI_{high}$ show if the child is close to critical values in blood already at a given (lower) age. We assumed that the intake from food or artificial milk after the end of breastfeeding was lower than or equal to 30 $ng{\cdot}kg^{-1}{\cdot}bw{\cdot}day^{-1}$ (this intake corresponds to the minimum risk level MRL (ASTDR, 2000)). We discuss mainly the results for TEDI values estimated for the HBM-I value (which are lower and therefore more protective than TEDIs estimated for HBM-II or CV). The recommended duration of breastfeeding and the proportion of nursing for partially breastfed or non-breastfed children from WHO (WHO, 2006) were used in the TEDI calculations (Table SM6). The sum of the iPCBs was used to calculate TEDIs because many countries use iPCBs for human monitoring (including breast milk), as has been recommended by the Stockholm Convention on Persistent Organic Pollutants for monitoring studies.

3. Results and discussion

3.1. Modelled total PCB concentrations

Modelled concentrations of total PCBs in children's blood lipids were computed for the four breastfeeding scenarios (see Section 2.3.1) and compared with the critical values of PCB concentrations in blood (Figs. 1 and SM1). Results from our model for the PRENATAL cohort and CZ-HBM show that nearly 26% and 80% of children have modelled blood PCB concentrations above the HBM-I value, 12% and 56% of children above the CV and 6.2% and 28.3% of children above the HBM-II value at nine months for the scenario with median breastfeeding.

At two years of age, 32%, 20.6% and 12.4% of the children from PRENATAL cohort exceeded HBM-I, CV and HBM-II values, with the maximum modelled concentration (3317 $ng{\cdot}g^{-1}_{lipid}$) almost five times higher than the CV for the scenario with reported breastfeeding. For the PRENATAL cohort, modelled concentrations using reported breastfeeding durations from questionnaires are very similar to modelled concentrations with median breastfeeding (Table SM7). With the breastfeeding duration from questionnaires, the modelled total PCB concentrations at age two are higher than in the median scenario of breastfeeding because a certain percentage of mothers in the Slovak population breastfed for more than nine months. The percentage of children above thresholds is almost twice as high at two years for the long breastfeeding scenario (Fig. 1) indicating a substantial effect of breastfeeding duration. For the CZ_HBM study, where we do not have information on breastfeeding duration from the questionnaires, the percentage of children who exceeded threshold values is somewhere between the median and high breastfeeding scenario, specifically, 83–95% of children are above HBM-I, 56–88% are above CV, and 25–75% are above HBM-II value at two years.

On the contrary, total PCB concentrations in the blood of non-breastfed infants or infants breastfed only for the first month gradually decrease (mainly due to rapid growth) (Fig. 1, the scenario with short breastfeeding). The CV and HBM II values are exceeded for those children only at the end of the first month in 1.4% and 0.7% of the cases, respectively. Modelled PCB Concentrations for each breastfeeding scenario, the age and the percentage of children above the critical blood PCB concentrations for the PRENATAL cohort and CZ-HBM are shown in Table SM7.

These high estimates of total PCB blood levels of breastfed children are no surprise considering the history of PCB production and use in the Czech and Slovak Republic. The model generally shows higher exposure of children from the Czech Republic than from Slovakia, which is due to almost twice higher measured PCB concentrations in breast milk from CZ-HBM than in the PRENATAL (Table SM1) cohort. The current PCB concentrations in breast milk in the Czech population are still high because the maximum of the exposure peak occurred more than 10 years later than in other European countries and spanned more than 10 years (Komprda et al., 2019).

From the modelled concentrations it can be seen that for the Czech and Slovak populations, adverse health effects in children due to PCB exposure are still possible although there has been a decline in PCB breast milk concentrations in the last decades (Banyiova et al., 2017). Early postnatal exposure in a Slovakian cohort (with PCB 153 serum concentrations in the range of our estimates) was associated with ototoxicity in toddlers (Koštiaková et al., 2016). Similarly, Dutta et al. (2012) found possible organ-specific effects, e.g., cardiotoxicity, hepatotoxicity and nephrotoxicity, in highly PCB-exposed children in Slovakia; postnatal PCB exposure was associated with

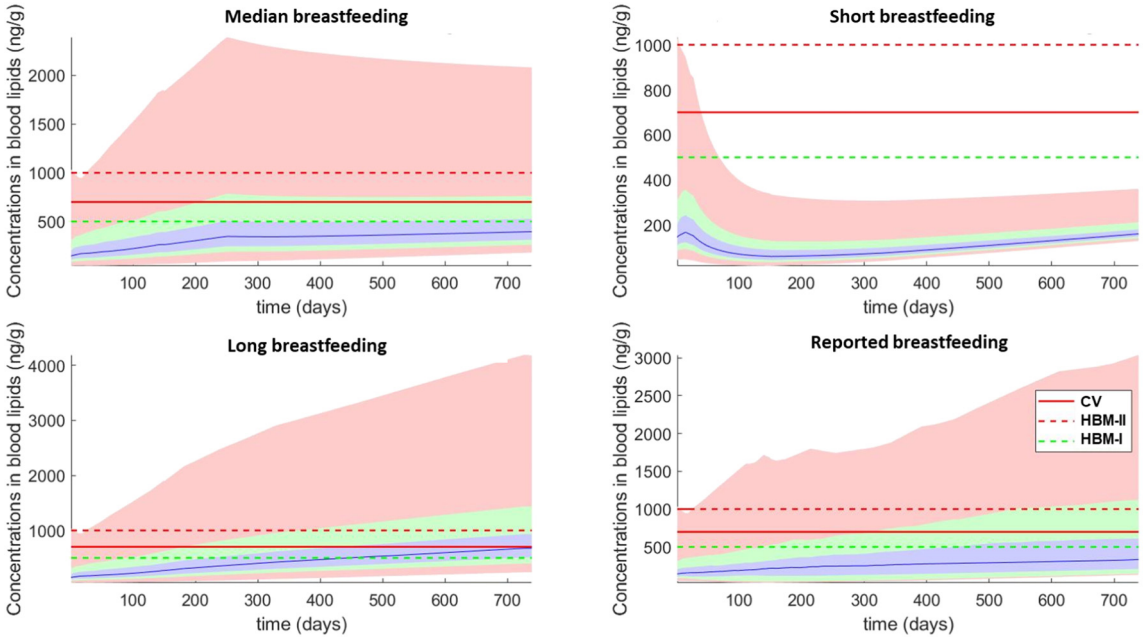

Fig. 1. Modelled concentrations of total PCBs in children's blood lipids for the PRENATAL cohort; the horizontal lines represent the threshold values of PCB blood concentration, HBM-I and HBM-II proposed by UBA and CV proposed by ANSES. The red range is 1%–99%, the green range is 10%–90%, the blue range is 25–75%, and the blue line is the median of the total PCB concentrations, calculated from the total number of children in the cohort.

poorer performance on otoacoustic tests in children at age 45 months (Jusko et al., 2014).

3.2. Threshold estimated daily intake for infants

Estimated daily intakes (EDIs) for each breastfeeding scenario, the age and the percentage of children above the threshold daily standards for the PRENATAL cohort and CZ-HBM are shown in Table SM8. The EDI results show a wide range of variability; they depend mainly on the duration of breastfeeding. The highest EDIs of iPCBs for both cohorts were reached during the first five months in fully breastfed infants. The EDI is in the range of 138–7581 ng·kg^{-1}bw·day^{-1}, with a median of 620 ng·kg^{-1} bw·day^{-1} in the first month for fully breastfed infants from the PRENATAL cohort. Values of EDIs in the first month are almost two times higher for CZ-HBM compared to PRENATAL, with a median of 1691 ng·kg^{-1}bw·day$^{-1,}$ and a range of 175–33,683 ng·kg^{-1}bw·day^{-1}, which is the result of the higher iPCB concentrations in breast milk from CZ-HBM in comparison to the Slovak cohort (Table SM1). EDI values of iPCBs gradually decline in the subsequent months because of the faster child growth and from the fifth month on mainly because of the introduction of food other than breast milk into children's diets. Median EDIs at age two are 154 ng·kg^{-1}bw·day^{1} (PRENATAL) and 304 ng·kg^{-1}bw·day^{-1} (CZ-HBM) for breastfed children (the scenario with long breastfeeding). For non-breastfed children, our EDIs of iPCBs are in the range of 2.4–4.7 ng·kg^{-1} bw·day^{-1} at three months of age for PRENATAL and CZ-HBM, given the relatively low PCB concentrations in infant formulas.

For fully or partially breastfed infants up to nine months, our EDI values exceed the MRL of 30 ng·kg^{-1}·bw·day^{-1} for total PCBs (ASTDR, 2000) and the TDI of 10 ng·kg^{-1}·bw·day^{-1} (RIVM) by an order of magnitude for the minimum EDI and by more than two orders of magnitude for the maximum EDI. A similar situation also exists in many other European countries; van den Berg et al. (2017) indicated that the ATSDR MRL was exceeded by one to two orders of magnitude for the countries included in the 4th/5th WHO Breast Milk Surveys (2005–2010), with the highest concentration of iPCBs in the Czech Republic and Slovakia.

The exceedances of the proposed safety standards by orders of magnitude indicate the problematic application of these limits to the breastfeeding period, so we calculated threshold estimated daily intakes (*TEDIs*) of iPCBs, which correspond to the threshold concentrations of total PCBs in children's blood.

Different $TEDI_{low}$ and $TEDI_{high}$ of iPCBs were calculated for different breastfeeding durations (Table 2). The $TEDI_{low}$ (HBM-I) is 110

Table 2
Threshold estimated daily intakes (*TEDI*) of iPCBs (ng·kg^{-1}·bw day^{-1}) for breastfed infants and toddlers. $TEDI_{low}$ is the mean daily intake for the duration of breastfeeding that leads to the threshold value of total PCB concentrations in blood in two years, $TEDI_{high}$ (in the brackets) is the mean daily intake for the duration of breastfeeding that leads to the threshold value of total PCB concentrations in blood already at a given age. $TEDI_{low}$ values for HBM-I are in bold.

Age	Breastfeeding[a]	$TEDI_{low}$ CV, $TEDI_{high}$CV	$TEDI_{low}$ HBM-II,$TEDI_{high}$ HBM-II	$TEDI_{low}$ HBM-I, $TEDI_{high}$ HBM-I
3 months	0–3 months (fully)	1030 (1920)	1520 (3130)	**220** (750)
6 months	0–6 months (fully)	620 (940)	880 (1510)	**190** (440)
9 months	0–9 months (6–9 partially)	420 (830)	590 (1240)	**160** (300)
12 months	0–12 months (6–12 partially)	310 (610)	460 (870)	**140** (220)
18 months	0–18 months (6–12 partially)	200 (230)	290 (430)	**120** (150)
24 months	0–24 months (6–24 partially)	150	210	**110**

[a] Duration of breastfeeding for $TEDI_{high}$ corresponds to the age when the child reaches the threshold values 700 ng·g^{-1} lipid (CV, ANSES, 2010), 1000 ng·g^{-1} lipid (HBM II, UBA, 2012), and 500 ng·g^{-1} lipid (HBM I, UBA, 2012), Intakes were rounded to the tens.

ng·kg^{-1}·bw·day^{-1} for children breastfed for two years (0–6 months fully and 6–24 partially; according to WHO recommendations), which means that a daily intake of iPCBs lower than 110 ng·kg^{-1}·bw·day^{-1} from birth to 2 years of age does not lead to an exceedance of the HBM-I blood value of 500 ng·g^{-1} lipids in serum (below which no adverse health effect is expected). However, the "allowable" intake from breast milk (which does not lead to exceeding the HBM-I value) may be higher if the breastfeeding period is shorter. Accordingly, for children breastfed for only 6 months, the $TEDI_{low}$ is 190 ng·kg^{-1}·bw·day^{-1}. Intake from breast milk during six months of breastfeeding should not exceed this value to avoid exceeding the HBM-I up to the age of two years. As mentioned above, we assume that the total intake from other sources (infant milk formula, food, air, dust) after the end of breastfeeding will not exceed the MRL of 30 ng·kg^{-1}·bw·day^{-1}, which is also consistent with our estimated range of 2.7–27 ng·kg^{-1}·bw·day^{-1} for non-breastfed children. Our $TEDI_{low}$ values for HBM-I are higher than the proposed TDI of 10 ng·kg^{-1}·bw·day^{-1} (RIVM) (Baars et al., 2001) and the MRL of 30 ng·kg^{-1}·bw·day^{-1} (ASTDR, 2000) but lower than the TDI of 400 ng·kg^{-1}·bw·day^{-1} accepted in the Czech Republic for children (Ruprich et al., 2011).

In addition to $TEDI_{low}$, we also calculated $TEDI_{high}$ values. The $TEDI_{high}$ represent the critical intake which leads to threshold concentrations (CV, HBM-I and HBM-II) of total PCBs at the end of breastfeeding (Table 2). For example, a mean iPCB daily intake of 440 ng·kg^{-1}·bw·day^{-1} in the first six months leads to the HBM-I blood value after these six months. Fig. SM2 shows the shape of estimated daily intakes of iPCB that lead to HBM-I threshold values of total PCB concentrations in blood at the end of breastfeeding and associated modelled total PCB concentrations in blood.

It is evident that intakes calculated for a specific age without including earlier exposure cannot be easily used for risk assessment because they underestimate exposure (e.g., the children's daily iPCB intake at two years of 27.2 and 30 ng·kg^{-1}·bw·day^{-1} is much lower than the mean daily intake over two years of 169 or 367 ng·kg^{-1}·bw·day^{-1}). Our *TEDIs* reflect children's physiological changes, change of lipids in breast milk during breastfeeding, intakes from all primary postnatal exposure sources (breast milk, food, dust, air), and prenatal exposure. The inclusion of prenatal exposure is important because children have certain PCBs concentration already at birth. The concentrations of the higher-chlorinated PCBs 138, 153 and 180 and PCB 118 in breast milk and cord blood are highly positively correlated (Table SM2). High inter-correlation between maternal blood, cord blood, and breast milk was also found in other studies (Ayotte et al., 2003; Grandjean et al., 2003). If the mother had a high PCB concentration in breast milk, the child's PCB exposure during pregnancy was also high, and the PCB concentration in a child can rapidly reach a threshold level.

As previously assessed, the benefits of breastfeeding far outweigh the toxicological harms associated with some POPs, even though the results show that maternal exposure to PCBs is still higher than that considered toxicologically safe for the fetus and the breastfed infant (van den Berg et al., 2017). However, given the fact that major neurodevelopment of children also takes place in the early years after birth and that the results of various studies point to a possible effect of perinatal exposure to PCBs (e.g. Dutta et al., 2012; Jusko et al., 2014; Koštiaková et al., 2016), especially for populations with higher PCB exposures, it is important to know the risks of exceeding safety standards.

The proposed TEDIs can be directly applied in risk assessment since iPCB breast milk monitoring is ongoing in many countries. Besides standardly used tolerable daily intakes for chronic exposure, the $TEDI_{low}$ for the threshold value of HBM-I (below which no adverse health effect is expected) can be considered as the limit of safe iPCB intake for the given duration of breastfeeding for children under two years of age. TEDIs can be compared with the intake of only three indicator PCBs 138, 153 and 180 because the difference between estimated total PCB exposure derived from 3 or 7 iPCBs is less than 4%. Additionally, *TEDIs* can also be used to approximate prenatal exposure and possible risk by, for example, comparing the estimated daily PCB intake from breast milk with the $TEDI_{high}$ value for the first months.

3.3. Exposure sources

Based on the modelled total PCB concentrations in children's blood, we calculated the contribution of individual sources of postnatal (breast milk, food, indoor dust, and indoor air) and prenatal exposure to PCBs for different scenarios of breastfeeding duration, according to the age of the children. Percentages of contributions are shown in Fig. 2 (PRENATAL cohort) and Fig. SM3 (CZ-HBM). Breast milk and prenatal exposure have the largest exposure contributions in breastfed infants under one year of age. According to our model, the contribution of breast milk (breastfeeding duration nine months; five exclusively and four partially) and transplacental transfer is together 71% (PRENATAL) and 85% (CZ-HBM) of PCB exposure in children at age two. For median breastfeeding, the breast milk contribution peaks at 88% (PRENATAL) and 91% (CZ-HBM) of total exposure at six months of age and remains high (65% for PRENATAL and 79% for CZ-HBM) even at two years of age. Prenatal exposure is around 43% (PRENATAL) and 38% (CZ-HBM) in the first month and gradually decreases to about 6–7% of total exposure at the end of the children's second year in both cohorts. At two years of age, the contribution of food is also significant, around 28% (PRENATAL) and 14% (CZ-HBM). In contrast, PCB contributions from dust and indoor air for all children, whether breastfed or not, are low, below 3% of total exposures, even at the end of the second year (Fig. 2). The contribution from dust and air is low despite the fact that we have slightly overestimated their PCB levels, because for both cohorts we used averages of concentrations for individual PCB congeners, which are higher than the medians.

Our findings are consistent with results from other studies. Prolonged breastfeeding was a major determinant of elevated higher-chlorinated PCB in children's blood up to 45 months of age in the Norwegian Mother and Child Cohort study (MoBa) (Caspersen et al., 2016) and in children in the Slovak cohort (Verner et al., 2013). Between 67% and 82% of the variability of PCBs (138, 153, 180) in blood of four-year-old children was explained by the maternal concentrations during pregnancy and the lactation period in the Spanish Asturias INMA cohort (Garí et al., 2019). Similarly, Jacobson et al. (1989) explained 60% of the variability in blood levels of Michigan children at four years of age based on maternal milk PCB levels and duration of breastfeeding. Also, in 7-year-old Faroese children, breastfeeding duration was the primary predictor of PCB blood levels

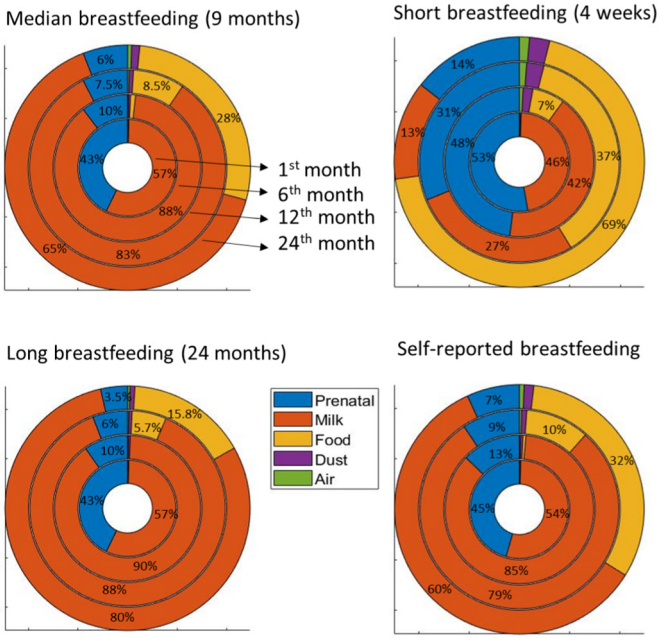

Fig. 2. Contribution of PCB exposure sources for different ages for the PRENATAL cohort; values below 3% are not displayed; individual breastfeeding scenarios are described in Section 2.3.1.

(Barr et al., 2006). Exclusive breastfeeding for more than three months was associated with twice as high PCB plasma concentrations in 7–10-year old children from Germany (Karmaus et al., 2001). Lanting et al. (1998) reported a mean PCB concentration 4.5 times higher in 42-month-old Dutch children breastfed for at least six weeks compared with those never breastfed.

Our model results also show that even short breastfeeding periods can significantly influence the PCB concentration at age two. The high contribution of breastmilk to total PCB exposure and the low contributions of air and dust fit with the paradigm suggested by Harrad and Diamond (2006) that exposure to persistent, bioaccumulative chemicals shifts from indoor/environmental sources to dietary sources with greater time from the period of peak chemical production and use. With more than 35 years since the end of PCB production in this region, exposures are driven by the persistent, hydrophobic and bioaccumulative properties of the chemicals, rather than primary emissions, leading to, in particular, high exposures via breastmilk.

3.4. Model validation and uncertainty

Our estimates of PCB exposure through breast milk are based on the modified PK model proposed by Stigum et al. (2015) and can be validated using data from the Slovakia PCB cohort (Forns et al., 2018). Forns et al. (2018) compared modelled PCB concentrations obtained by their pharmacokinetic model with concentrations measured in the serum of 311 and 308 children at age 6 and 16 months from the Slovakia PCB cohort. The explained variability from linear regressions for log-transformed PCB-153 concentration (modelled vs. measured) was 0.61 at 6 months and 0.67 at 16 months (Forns et al., 2018). These values are similar to those obtained from a physiologically based PK model published by Verner et al. (2013) for the Slovakia PCB cohort (Hertz-Picciotto et al., 2003).

Because we modified the PK model slightly and added exposure from other sources, we additionally used a subset of data ($N = 60$) from the same Slovakia PCB cohort (Hertz-Picciotto et al., 2003) as Forns et al., 2018 to validate the model. For this subset of data, indoor air and dust samples were collected in 2015 from the households of participants who participated in the Slovakia PCB risk cohort (Demirtepe et al., 2019). Concentrations of PCBs were measured in those samples and used in our validation. The explained variability between measured and modelled log-transformed PCB 153 concentrations in serum at 6 and 16 months from linear regression is 0.82 and 0.77 (Fig. SM4). This is a higher agreement than was obtained by Forns et al. (2018), which may be due to a more accurate model parameterization or because we used a smaller number of samples (and therefore have less variability in our data). We added intakes from food, air, and dust to our PK model. Especially for children breastfed for a shorter period, the addition of intake from food can improve the model results while intake from air and dust is negligible. The model slightly overestimates the lower concentrations (Fig. SM4). Part of the variability between modelled and measured concentrations may be due to variability in partial breastfeeding, length of use of infant milk formulas or introduction of foods where we do not have individual information. For example, from the questionnaires we obtained data about partial and full breastfeeding in weeks. However, the exact percentage of partial breastfeeding compared to infant milk formula or later complementary food is unknown. In our model, the proportion of breast milk is 50% in the first five months if the infant was partially breastfed. However, this percentage (and hence the PCB concentration) in partially breastfed infants may be lower.

For Stigum's and Verner's PK models, concentrations in blood or breast milk can be used as an input. This approach is applicable to higher-chlorinated PCBs (e.g., PCB 138, 153, 180), where cord/maternal blood concentrations are highly correlated with concentrations in breast milk. On the other hand, there is a very low or no correlation in the case of lower-chlorinated PCBs (PCB 28, 52 and 101) (Table SM2). For these congeners, it is important to add to the model both concentrations in cord blood as initial exposure during the prenatal period and concentrations in breast milk that reflect actual daily intake during postnatal exposure. For the PRENATAL cohort, measured concentrations in cord blood and breast milk were used for all PCBs in our model. However, cord blood PCB concentrations were not available for children from CZ-HBM. These concentrations were estimated for lower-chlorinated PCBs as medians (PCBs 52 and 101) or using the regression equations for PCB 28 (with a lower explained variability of 0.37) (Table SM2). This approximation should not significantly influence results because lower-chlorinated PCB contribution to the total sum of indicator PCB is relatively small and accounted for approximately 10% at two years of age (for reported, median, and long breastfeeding scenarios). Because the lipid composition differs between blood and breast milk or adipose tissue (fat), the fraction of neutral lipid equivalents in blood was used in the PK model (for details see SM).

4. Conclusion

The high percentage of children under two years of age who are above critical PCB blood levels in the exposed Czech and Slovak population indicates a constant need for PCB monitoring. The analysis of the exposure sources shows that air and dust exposure is negligible for children and the main focus should be on reducing maternal exposure through food. Established tolerable daily intake standards set mainly for chronic daily exposure do not reflect the internal body burdens caused by past exposure and possible risk from relatively high PCB intake during breastfeeding. As a result, tolerable daily standards are often exceeded in infants and toddlers, but it is not clear how much risk this exceedance poses to children. We derived new PCB threshold estimated daily intakes (*TEDIs*) for breastfed infants and toddlers, which correspond to critical PCB concentrations in the blood during the first two years of life. Besides the tolerable daily intakes for chronic exposure, our $TEDI_{low}$ can be considered as threshold for safe iPCB intakes for infants and toddlers and $TEDI_{high}$ can serve as threshold daily intakes over which adverse health effects for a breastfeeding period cannot be excluded.

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CRediT authorship contribution statement

KK: study design, literature research, statistical analyses, model programming and validation, interpretation of results, manuscript writing, manuscript editing and validation.

EDR, BMS, LM: literature research, feedback on the interpretation of results, manuscript writing/editing/validation.

JK: model programming and validation, interpretation of results, manuscript editing and validation.

MS: feedback on the interpretation of results, manuscript editing / validation.

KČ, BD, AF: laboratory analysis-processing, analysis and evaluation of blood serum and breast milk samples from the PRENATAL cohort, feedback on the interpretation of results, manuscript editing.

ĽPM, TT: study design, management and coordination of the PRENATAL cohort, feedback on the interpretation of results, manuscript editing.

MČ: study design, management and coordination of the CZ-HBM, feedback on the interpretation of results, manuscript editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.154734.

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