Coupled mother–child model for bioaccumulation of POPs in nursing infants

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This paper addresses a model for accumulation of organic compounds by mother and breast-fed infant,
applicable for exposure assessment within larger frameworks.

Abstract

Bioaccumulation of persistent organic pollutants (POPs) leads to high levels in human milk and high doses of POPs for nursing infants. This is currently not considered in chemical risk assessment. A coupled model for bioaccumulation of organic chemicals in breast-feeding mother and nursing infant was developed and tested for a series of organic compounds. The bioaccumulation factors (BAFs) in mother, breast milk and child were predicted to vary with log K_{OW} and, for volatile compounds, with K_{AW} and concentration in air. The concentrations of POPs in the infant body increase the first half year to about factor 3 above mother and decline thereafter to lower levels. The predicted results are close to empirical data and to an empirical regression. The new mother–child model is compact due to its easy structure and the analytical matrix solution. It could be added to existing exposure and risk assessment systems, such as EUSES.
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1. Introduction

Persistent organic pollutants (POPs) are "chemicals that remain intact in the environment for long periods, become widely distributed geographically, accumulate in the fatty tissue of living organisms, and are toxic to humans and wildlife" (UNEP, 2007). POPs, such as polychlorinated dibenzodioxins and dibenzofurans (PCDD/F), polychlorinated biphenyls (PCB) and chloroorganic pesticides, have been detected in human milk samples all over the world (Rogan et al., 1986; Schecter et al., 1996; Filser et al., 1997; Raab et al., 2007; Shen et al., 2007; Wittsiepe et al., 2007; Tanabe and Kunisue, 2007). This raised considerable concern about adverse health effects on nursing infants (Harrison, 2001; CEHAPE, 2004; US EPA, 2006).

The uptake of POPs, such as PCDD/F, by adults is mainly via food ingestion (Travis and Hattemeyer-Frey, 1991). The uptake by nursing infants via breast milk has been reported to be higher than by adults via diet, for some POPs at levels above the acceptable daily intake (Dahl et al., 1995; Kreuzer et al., 1997; Schade and Heinzow, 1998; BgVV, 2000; Tanabe and Kunisue, 2007). POPs may accumulate for a longer period in the body of the mother and then be transferred to the nursing infant via mother's milk. Travis et al. (1988) developed empirical relations for the accumulation of chemicals in human adipose tissue and human milk. The regressions are based on 12 (tissue) or six (milk) organic chemicals with a log K_{OW} between 1.32 and 6.50 (tissue) or 5.16–6.50 (milk). The bioaccumulation factors B_f (tissue) and B_m (milk) were defined as

$$B_f = \frac{\text{concentration of organic in adipose tissue } (\text{mg kg}^{-1} \text{ lipid})}{\text{average daily intake of organic } (\text{mg d}^{-1})}$$

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$$B_\text{m} = \frac{\text{concentration of organic is breast milk } \left(\text{mg kg}^{-1} \text{ lipid}\right)}{\text{average daily intake of organic } \left(\text{mg d}^{-1}\right)}$$

Travis et al. (1988) related these bioaccumulation factors to the log K_OW of the substances.

$$B_\text{f} = 2.0 \times 10^{-4} K_\text{OW}^{1.05} \quad \left[\frac{\text{d}}{\text{kg}}\right] \quad (n = 12, r = 0.98)$$

$$B_\text{m} = 9.8 \times 10^{-5} K_\text{OW}^{1.14} \quad \left[\frac{\text{d}}{\text{kg}}\right] \quad (n = 6, r = 0.97)$$

Besides this empirical approach, several mathematical model approaches exist to predict human tissue concentrations after uptake, e.g., the models prepared by Kreuzer et al. (1997) or Filser et al. (1997) and Maruyama et al. (2003) for PCDD/F. Accumulation in the food chain with subsequent accumulation in humans was addressed by Czub and McLachlan (2004a,b). To summarize, compound-specific models, comprehensive numerical models and also easy empirical models for the prediction of the accumulation of POPs in humans are available.

However, what lacks is a model predicting accumulation of POPs or other compounds in breast-feeding mother and nursing infant after uptake of chemicals via diet or other relevant sources by mother, which is compact enough to be combined with other models and estimation routines, e.g., for chemical safety assessment tools such as EUSES (EC, 1996).

"Traditional risk assessment approaches and environmental health policies have focused mainly on adults and adult exposure patterns, utilizing data from adult humans or adult animals" (CEHAPE, 2004). Indeed, current chemical risk assessment in the EU (EC, 2003) considers only grown-ups (70 kg bodyweight). An additional focus on children and in particular nursing infants, which are one trophic level higher and are eventually also more sensitive to chemicals, requires a compact exposure estimation method that can run with a minimum data set.

This paper addresses the development, parameterization, sensitivity analysis, validation and application of a coupled model for accumulation of organic compounds by nursing mother and child. The coupled differential equations were solved analytically. The model was tested with 2,3,7,8-TCDD and compared to empirical data for 11 other compounds collected by Travis et al. (1988).

2. Methods

2.1. Model development

Fig. 1 gives an overview of the system considered by the model. The human body is considered as a flux-through system. The input of chemical occurs via diet (mother) or milk (child) and inhalation (both). Inside the body, phase equilibrium is assumed. The compound is eliminated from the body by exhalation and excretion (both together are named "outflux"), by metabolism and, in case of the nursing mother, with breast milk.
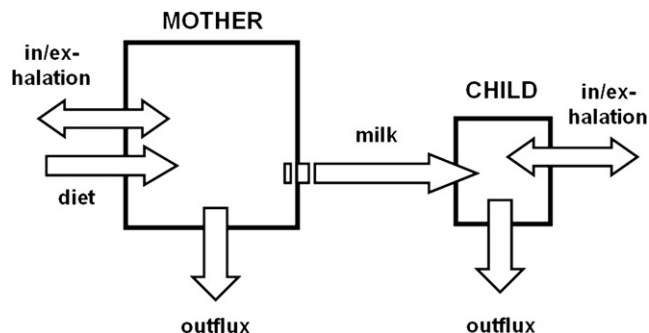

Fig. 1. System overview.

2.1.1. Mother before birth of the child

The input of chemical into the mother is independent of the concentration in her body, C_H, while the output is proportionally related to it. This yields a linear differential equation for the mass balance of the form

$$\frac{\text{d}m}{\text{d}t} = I - km \tag{1}$$

where m [mg] is the mass of chemical in the human body, I [mg d^{-1}] is the sum of daily uptake of chemical and k [d^{-1}] is the loss rate constant.

The input I can be derived from measurements or exposure assessments. The loss rate constant k is calculated from the flux of chemical out of the body.

The human body is considered as composed of lipids and water phases. Lipids were assumed to have properties similar to octanol. The phase equilibrium between concentration in human body, C_H [mg kg^{-1}], and concentration in water, C_W [mg L^{-1}], is

$$K_\text{HW} = \frac{C_\text{H}}{C_\text{W}} = W_\text{H} + \frac{L_\text{H}}{\rho_\text{L}} K_\text{OW} \quad \left[\frac{\text{L}}{\text{kg}}\right] \tag{2}$$

where K_HW is the partition coefficient human body to water [L kg^{-1}], W_H is the water content [L kg^{-1}] and L_H is the lipid content of the human body [kg kg^{-1}], ρ_L is the density of lipids [kg L^{-1}] and K_OW [L L^{-1}] is the partition coefficient between octanol and water.

The change of chemical mass in time due to outflux of chemical from the body $\text{d}m_\text{F}/\text{d}t$ [mg d^{-1}] is the sum of outflux with water, lipid and air

$$\frac{\text{d}m_\text{F}}{\text{d}t} = F_\text{W} C_\text{F,W} + F_\text{L} C_\text{F,L} + F_\text{A} C_\text{F,A} = F C_\text{F} \quad \left[\frac{\text{mg}}{\text{d}}\right] \tag{3}$$

where F_W is the outflux of water [L d^{-1}], F_L is the outflux of lipids [kg d^{-1}] (with feces) and F_A is the outflux of air [L d^{-1}] (exhalation). $C_\text{F,W}$ [mg L^{-1}], $C_\text{F,L}$ [mg kg^{-1}] and $C_\text{F,A}$ [mg L^{-1}] are the concentrations in the water, lipid and gas fraction of the outflux; C_F [mg kg^{-1}] is the weighted average concentration in the outflux. The total material outflux, F [kg d^{-1}], is the sum of the outfluxes of water, lipids and air,

$$F = F_\text{W} \rho_\text{W} + F_\text{L} + F_\text{A} \rho_\text{A} \quad \left[\frac{\text{kg}}{\text{d}}\right] \tag{4}$$

Using the assumption of phase equilibrium we can rewrite to

$$F C_\text{F} = F f_\text{W} C_\text{F,W} + F f_\text{L} K_\text{OW} C_\text{F,W} + F f_\text{A} K_\text{AW} C_\text{F,W} \tag{5}$$

where K_AW is the partition coefficient [L L^{-1}] between air and water (also known as dimensionless Henry's Law constant), and f are the flux fractions [L d^{-1}:kg d^{-1}] of water (W), lipids (L) and air (A) of the total flux F,

$$f_\text{W} = \frac{F_\text{W}}{F}, f_\text{L} = \frac{F_\text{L}/\rho_\text{L}}{F}, f_\text{A} = \frac{F_\text{A}}{F} \quad \left[\frac{\text{L}}{\text{kg}}\right] \tag{6}$$

The average concentration of chemical in the outflux, C_F, is then

$$C_\text{F} = f_\text{W} C_\text{F,W} + f_\text{L} K_\text{OW} C_\text{F,W} + f_\text{A} K_\text{AW} C_\text{F,W} \tag{7}$$

Note that for phase equilibrium, $C_{F,W}$ (concentration in aqueous phase of out-flux) equals C_W (concentration in aqueous phase of human body), and thus we derive

$$K_{FW} = \frac{C_F}{C_W} = f_W + f_L K_{OW} + f_A K_{AW} \quad \left[\frac{L}{kg}\right] \tag{8}$$

where K_{FW} [L kg^{-1}] is the partition coefficient between outflux [kg d^{-1}] and water [L d^{-1}]. Then, the partition coefficient between human body and outflux, K_{HF} [kg kg^{-1}], is

$$K_{HF} = \frac{C_H}{C_F} = \frac{K_{HW}}{K_{FW}} \quad \left[\frac{kg}{kg}\right] \tag{9}$$

where C_H and C_F are the concentrations [mg kg^{-1}] in human body and outflux in phase equilibrium. It follows for the loss rate constant k [d^{-1}] in Eq. (1), which is the sum of the losses by outflux and by metabolism or degradation with first-order k_{deg} [d^{-1}]

$$k = \frac{F}{M_H K_{HF}} + k_{deg} \quad \left[\frac{1}{d}\right] \tag{10}$$

where M_H [kg] is the bodyweight. The analytical solution of Eq. (1) for the chemical mass m [mg] in human body at time t is

$$m(t) = m_0\, e^{-kt} + \frac{I}{k}\left(1 - e^{-kt}\right) \tag{11}$$

which gives in steady-state ($t \to \infty$)

$$m(\infty) = \frac{I}{k} \tag{12}$$

Concentrations C_H [mg kg^{-1}] in the human body were derived from $C_H = m/M_H$, assuming a constant bodyweight M_H

$$C_H(\infty) = \frac{m(\infty)}{M_H} = \frac{I}{k M_H} \quad \left[\frac{mg}{kg}\right] \tag{13}$$

This solution was used to calculate the concentration of chemical in the woman before birth of the child (and before pregnancy, the bodyweight is constant at 60 kg).

2.1.2. Nursing mother with child

In this scenario, the mother gives birth to a child and nurses the infant. Equations for the mother were modified, and new equations for breast milk and nursing child were introduced.

2.1.2.1. Mother.
Nursing changes the outflux from the mother. Milk consists in the model of water and lipids. The flux of milk F_M [kg d^{-1}] was added to the outflux F in Eq. (4)

$$F = F_W \rho_W + F_L + F_A \rho_A + W_M \rho_M F_M + L_M F_M \quad \left[\frac{kg}{d}\right] \tag{14}$$

where W_M [L kg^{-1}] is the water content and L_M [kg kg^{-1}] is the lipid content of human milk. Fractions of outflux [L kg^{-1}] f_W, f_L and f_A were recalculated for the case of nursing.

$$f_W = \frac{F_W + W_M F_M}{F}, f_L = \frac{F_L + L_M F_M}{F \rho_L} \text{ and } f_A = \frac{F_A}{F} \quad \left[\frac{L}{kg}\right] \tag{15}$$

The other equations (Eqs. (1), (2), (8)−(13)) were applied without changes, but the new values of F and f were entered.

2.1.2.2. Milk.
With breast milk, chemical is lost from the mother and transferred to the baby (Schecter et al., 1996). To calculate the concentration of chemical in milk, phase equilibrium between milk and mother was assumed. The concentration in milk C_M [mg kg^{-1}] is

$$C_M = K_{MH} C_H \quad \left[\frac{mg}{kg}\right] \tag{16}$$

where K_{MH} [kg kg^{-1}] is the partition coefficient between milk and human. The partition coefficient milk to water K_{MW} [L kg^{-1}] is

$$K_{MW} = \frac{C_M}{C_W} = W_M + \frac{L_M}{\rho_L} K_{OW} \quad \left[\frac{L}{kg}\right] \tag{17}$$

The partition coefficient between milk and human body K_{MH} [kg kg^{-1}] is then

$$K_{MH} = \frac{C_M}{C_H} = \frac{K_{MW}}{K_{HW}} \quad \left[\frac{kg}{kg}\right] \tag{18}$$

2.1.2.3. Child.
The breast-fed infant can take up chemicals by breast milk and by inhalation. Breathing is external input to the child, $I_C = F_A C_A$, where F_A [here: m^3 d^{-1}] is the flux of inhaled air and C_A [mg m^{-3}] is the concentration of chemical in air. Loss of chemical occurs via outflux and by metabolic elimination with first-order rate constant k_{deg} [d^{-1}]. The mass balance for the child is

$$\frac{dm_C}{dt} = I_C + C_M F_M - C_F F_C - k_{deg} m_C \tag{19}$$

where C_M [mg kg^{-1}] denotes the concentration in breast milk, F_M [kg d^{-1}] is the flux of milk from mother to child, C_F [mg kg^{-1}] is the concentration in the outflux of the child and F_C [kg d^{-1}] is the outflux from the child.

Using the partition coefficients, the equation can be rewritten to

$$\frac{dm_C}{dt} = I_C + K_{MH} \frac{F_M}{M_H} m_H - \frac{F_C}{K_{CF} M_C} m_C - k_{deg} m_C \quad \left[\frac{mg}{d}\right] \tag{20}$$

where m_H [mg] is the chemical mass in mother (human H), m_C [mg] is the chemical mass in the child, K_{CF} [kg kg^{-1}] is the partition coefficient between child and outflux and M_C [kg] is the body mass of the child. The phase equilibrium between child body (index C) and water (index W) is

$$K_{CW} = \frac{C_C}{C_W} = W_C + \frac{L_C}{\rho_L} K_{OW} \quad \left[\frac{L}{kg}\right] \tag{21}$$

where K_{CW} [L kg^{-1}] is the partition coefficient child body to water, C is the equilibrium concentration in child, index C [mg kg^{-1}], or water, index W [mg L^{-1}], W_C [L kg^{-1}] is the water content and L_C [kg kg^{-1}] is the lipid content of the child body. The initial concentration in the child C_C (0) [mg kg^{-1}] was calculated from phase equilibrium to mother

$$C_C(0) = \frac{K_{CW}}{K_{HW}} C_H \tag{22}$$

The outflux F_C [kg d^{-1}] from the child was summed up, as was done for the outflux from the mother:

$$F_C = F_W \rho_W + F_L + F_A \rho_A \tag{23}$$

where indices W, L and A indicate water, lipid and air. Again, the flux fractions were used to calculate the phase equilibrium between outflux and water, K_{FW}:

$$K_{FW} = \frac{C_F}{C_W} = f_W + f_L K_{OW} + f_A K_{AW} \quad \left[\frac{L}{kg}\right] \tag{24}$$

The partition coefficient between child body and outflux, K_{CF} [kg kg^{-1}], is

$$K_{CF} = \frac{C_C}{C_F} = \frac{K_{CW}}{K_{FW}} \quad \left[\frac{kg}{kg}\right] \tag{25}$$

2.2. Matrix solution

The differential equations of mother and child are coupled and were treated as a linear 2 × 2 matrix system of the form

$$\frac{dm_1}{dt} = a_{11} m_1 + a_{12} m_2 + I_1 \tag{26}$$

$$\frac{dm_2}{dt} = a_{21} m_1 + a_{22} m_2 + I_2 \tag{27}$$

Matrix element 1 is the mother. The matrix constant a_{11} [d^{-1}] is the sum of all loss processes from the mother and is identical with the negative loss rate k

(Eq. (10)). The matrix constant a_{12} [d^{-1}] is what mother receives from the child and is zero (therefore, the equation for chemical mass in mother can be solved independently of that for the child, Eqs. (1) and (11)). Input I_1 [mg d^{-1}] is the sum of all input to mother.

Matrix element 2 is the nursed child. The matrix constant a_{21} [d^{-1}] describes the transfer via milk from mother to child, $a_{21} = K_{MH} \times F_M/M_H$. The matrix constant a_{22} [d^{-1}] describes all losses of chemical from the child, $a_{22} = -F_C/(K_{CF} \times M_C) - k_{deg}$. Input I_2 includes all chemical input independent from the mother, i.e. via inhalation, $I_2 = F_A \times C_A$. A standard solution for this system of differential equations exists for the case of constant rates and inputs (Nazaroff and Alvarez-Cohen, 2001). Concentrations [mg kg^{-1}] were derived by dividing the chemical mass [mg] by the bodyweight [kg].

2.3. Parameterization of the model

Input data (Table 1) were selected from several sources, preferably from existing models (Kreuzer et al., 1997; Czub and McLachlan, 2004b), in order to allow a comparison of the results. The application of the steady-state solution (Eqs. (12) and (13)) for the mother before the birth of her child avoids the need to choose an appropriate initial mass m_0 for the first generation. The 95% steady-state is reached for latest $t = 18$ years for all chemicals with the default parameterization.

The total daily uptake I [mg d^{-1}] was calculated as the sum of uptake via diet i_D [mg d^{-1}] and inhalation of air:

$$I = i_D + F_A C_A \quad \left[\frac{\text{mg}}{\text{d}}\right] \tag{28}$$

For the breast-fed baby, i_D is 0.

Table 1
Default input data for the mother–child model

Parameter	Symbol	Value	Unit	Reference
Mother				
Age	t	25	a	Kreuzer et al. (1997)
Body mass	M_H	60	kg	Maruyama et al. (2003)
Body water fraction	W	0.71	L kg^{-1}	Czub and McLachlan (2004b)
Body lipid fraction	L	0.284	kg kg^{-1}	Deurenberg et al. (1991)
Outflow of water	F_W	1.24	L d^{-1}	Maruyama et al. (2003)
Outflow of lipid	F_L	0.007	kg d^{-1}	10% of lipids in diet
In/exhalation of air	F_A	11	m^3 d^{-1}	Layton (1993)
Breast milk data				
Milk flux	F_M	1	kg d^{-1}	Kreuzer et al. (1997)
Milk water content	W_M	0.87	L kg^{-1}	Czub and McLachlan (2004b)
Milk lipid content	L_M	0.045	kg kg^{-1}	Kreuzer et al. (1997)
Child				
Age	t	0–3	a	
Body mass	M_b	3.5–7.25	kg	Hesse et al. (1997)
Body water fraction	W	0.71	L kg^{-1}	Czub and McLachlan (2004b)
Body lipid fraction	L	0.233	kg kg^{-1}	Deurenberg et al. (1991)
Outflow of water	F_W	0.87	L d^{-1}	water content of 1 kg milk
Outflow of lipid	F_L	0.0045	kg d^{-1}	10% of influx
Outflow of air	F_A	4.5	m^3 d^{-1}	Layton (1993)
Other data				
Density of water	ρ_W	1	kg L^{-1}	
Density of lipids	ρ_L	0.82	kg L^{-1}	
Density of air	ρ_A	1.3×10^{-3}	kg L^{-1}	

Outflux of lipids was assumed to be 10% of lipids in the diet. With 70 g d^{-1} as average lipid ingestion, 0.007 kg d^{-1} outflux of lipids results. For the baby, 0.0045 kg d^{-1} (1/10 of influx of lipids with milk) was used. Table 1 lists the input data chosen as default for the model and used in the following simulations.

To calculate concentrations in the body of the child during the simulation period, the respective bodyweight was used, to account for growth effects. The bodyweight of the child with age (in years) was approximated by a second-order polynom fitted to growth data for girls in Germany (Hesse et al., 1997) (Eq. (29))

$$\text{bw} = -0.053 \times \text{age}^2 + 3.76 \times \text{age} + 3.54 \quad (n = 36, R^2 = 0.98) \tag{29}$$

3. Results

3.1. Example simulation TCDD

To illustrate the general behaviour of the model, an example simulation with 2,3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD) was performed. TCDD is a highly toxic, persistent lipophilic (log K_{OW} 6.76) and semivolatile (K_{AW} 0.0015) compound (Rippen, 1990–2007). The concentration of TCDD in air was set to 4 fg m^{-3} (background concentration in Southern Germany, McLachlan, 1992). Ingestion of TCDD by the mother with diet was 25 pg d^{-1} (Kreuzer et al., 1997). Fig. 2 shows the simulated concentration of TCDD in lipids for mother and child over a 3-year period. The starting concentration of the mother [3.6 ng kg^{-1} lipid] is the steady-state concentration (Eq. (13)). For $t > 0$, the matrix solution was applied. For $t > 0$, the concentration of TCDD in mother decreases exponentially and falls to 63% of the initial concentration after 0.5 year and to 42% after 1 year of nursing. The initial concentration in the infant [3.6 ng kg^{-1} lipid] is in equilibrium to mother. It steeply increases to 12.3 ng kg^{-1} lipids after 0.5 year. Hereafter, it falls, due to depletion of the mother's body burden and growth dilution, to 8.8 ng kg^{-1} lipids after 1 year and to 1.73 ng kg^{-1} lipid after 3 years (of course, 3 years of nursing is rare). The concentration in lipids of milk is identical to that in lipids of the mother's body and was not plotted.
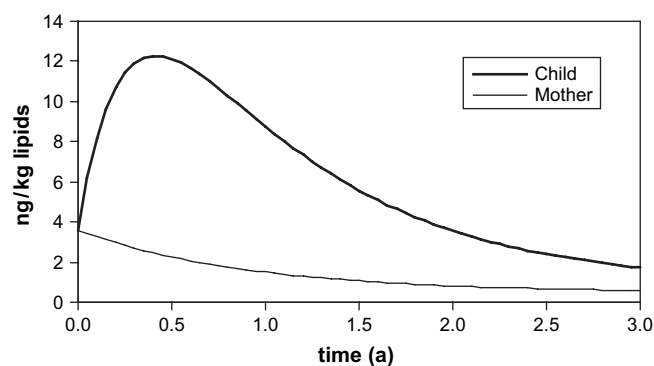

Fig. 2. Concentrations in nursing mother and child (ng kg^{-1} lipids) after uptake of 25 pg TCDD per day with diet by the mother.
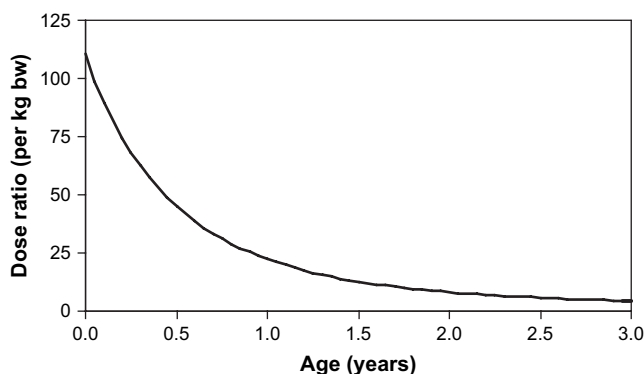
Fig. 3. Ratio of the TCDD-dose taken up by the nursing infant (per kg bw) to the dose taken up by the mother ($25 \text{ pg d}^{-1} = 0.42 \text{ pg kg}^{-1} \text{ bw d}^{-1}$).

Fig. 4. Calculated bioaccumulation factor (BAF) mother ($t = 0$) and milk ($t = 0.5$ a) with varying log K_{OW} for low K_{AW} ($K_{AW} = 10^{-9} \text{ L L}^{-1}$) and high K_{AW} ($K_{AW} = 0.1 \text{ L L}^{-1}$) compared to the result derived with the regression of Travis et al. (1988).

During the period of nursing, the loss of TCDD from mother with milk is higher than the daily intake, which is the reason for the depletion of TCDD from the body of the mother.

Fig. 3 shows the ratio of the TCDD-dose taken up by the infant (per kg bw) divided by the dose taken up by the mother ($25 \text{ pg d}^{-1} = 0.42 \text{ pg kg}^{-1} \text{ bw d}^{-1}$). The ratio is initially 110 and falls later to 45 ($t = 0.5$ a), 22 ($t = 1$ a) and 4.5 ($t = 3$ a). The dose ratio is much higher than the concentration ratio (Fig. 2). Uptake of TCDD with air is neither for mother (inhalation 11 m^3 per day, uptake 44 fg TCDD per day) nor infant (inhalation 4.5 m3 per day, uptake 18 fg TCDD per day) of relevance. The maximum concentration ratio child to mother is reached after $t = 0.5$ a. The concentration in the child is maximally 3.4 times that in mother before birth and falls to 2.5 times ($t = 1$ a) and to 0.48 times ($t = 3$ a), due to rapid elimination and growth dilution. The calculated elimination half-time (ln 2 divide by rate constant k) of TCDD from the body is 4.6 years for the mother before birth, 0.6 years for the nursing mother and only 0.34 years for the infant.

These simulation results can be confronted to empirical data (Kreuzer et al., 1997; Filser et al., 1997). Measured concentrations of TCDD in lipids of adipose tissue and blood for adults in Germany in early 1990s range from $<0.1 \text{ ng kg}^{-1}$ lipids to 16 ng kg^{-1} lipids, with an average background level of 3 ng kg^{-1} lipids (Filser et al., 1997). Concentrations in breast milk vary between 1 and 3.9 ng kg^{-1} lipids, decreasing during the period of nursing, with an average of about 2 ng kg^{-1} lipids. TCDD concentrations in stillborn range from 1.3 to 2.1 ng kg^{-1} lipids. Concentrations of TCDD in lipids of adipose tissue, faeces and blood of infants did not differ much and ranged from <0.2 to 7.3 ng kg^{-1} lipids. TCDD levels in adipose tissue of 20 breast-fed infants aged between 0 and 44 weeks ranged from 0.16 to 4.1 ng kg^{-1} tissue and were higher than that of non-breast-fed children (0.16–0.76 ng kg^{-1} lipids) (Kreuzer et al., 1997). Predicted half-life of TCDD in infants was short (0.42 years), and increased to about 10 years for adults between 40 and 60 years of age. These results are throughout close to the outcome of the simulations with the mother–child model, without any conflicting results.
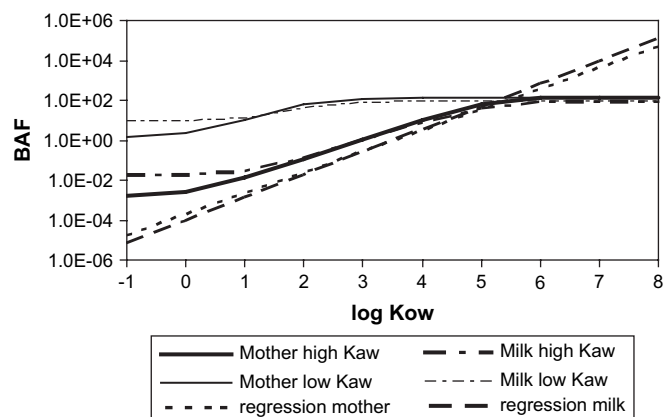
4. Discussion

4.1. Comparison of regression and mother–child model

The regression of Travis et al. (1988) uses only one physico-chemical parameter, the K_{OW}, while the mother–child model requires K_{OW} and K_{AW}. The bioaccumulation factors (BAFs), related to concentration in lipids, derived from model and regression were compared. The concentration in air was set to 0. The steady-state BAF of mother at birth of the child ($t = 0$) and the BAF milk after $t = 0.5$ year were plotted in Fig. 4. The BAFs for mother and milk are practically identical, except for very hydrophilic compounds (the relation to lipids gives artificially higher concentrations for milk if compounds do not partition into lipids). The model BAFs differ more than two orders of amount with low (10^{-9}) or high (0.1) K_{AW} except for high log K_{OW}, because volatile compounds are rapidly lost from the body via exhalation. Within its regression range (log K_{OW} 1.32–6.50), the regression gives similar results as the model with high K_{AW}, probably because the less lipophilic compounds in the training set of the regression were all solvents with high K_{AW} (Table 2). With increasing lipophilicity, the BAFs predicted by the mother–child model reach a plateau (mother at $t = 0$: BAF is 143 [d kg^{-1} lipid], milk at $t = 0.5$ years: BAF is 90 [d kg^{-1} lipid]), while the BAFs derived by the regression increase unlimited with K_{OW}. This is unrealistic, except for short time-periods, as the loss of super-lipophilic compounds via milk would be several orders of amount higher than the daily intake. The daily intake (1 mg d^{-1}) is balanced at a BAF milk (4.5% lipids) of 22 [d kg^{-1} lipid]. The regression gives a BAF = 22 [d kg^{-1} lipid] with log $K_{OW} = 4.7$, but higher BAF for all log K_{OW} above that value. On the contrary, the steady-state ($t = \infty$) BAF milk predicted by the mother–child model for compounds with log $K_{OW} > 4.7$ is constant at 19 [d kg^{-1} lipid]. In the initial period of nursing, the BAF milk is above steady-state, therefore, mother is depleted from POPs by nursing (Fig. 2).

Table 2
Names and physico-chemical data of the compounds in Travis et al. (1988)

Abbreviation	Compound	log K_{OW}[a]	K_{AW}[b]
Benzene	Benzene	2.13	0.23
DDE	1,1-Bis(4-chlorphenyl)-2,2-dichloroethene	5.83	0.05
DDT	1,1-Bis(4-chlorphenyl)-2,2,2-trichlorethan	5.76	0.0016
DCM	Dichlormethane	1.32	0.087
Dieldrin	Dieldrin	5.16	0.0044
HE	Heptachlor epoxide	5.40	0.01
HCB	Hexachlorbenzene	5.45	0.028
PCE	Perchlorethene	2.53	0.54
PCB	Polychlorinated biphenyls	6.50	0.001[c]
TCE	Trichlorethene	2.33	0.35
MC	Methylchloroform	2.47	0.715
TCDD	2,3,7,8-Tetrachlordibenzo-*p*-dioxin	6.76[b]	0.0015

[a] Travis et al. (1988) if not given otherwise.
[b] Rippen (1990–2007) if not given otherwise.
[c] Estimate; PCB is a mix of 209 compounds.

4.2. Uptake via inhalation compared to uptake via food

The impact of exhalation on BAF of hydrophilic to medium lipophilic compounds (log K_{OW} < 5) is evident from Fig. 4: fugitive compounds with high K_{AW} show much lower bioaccumulation, due to this process. On the other hand, the K_{AW} may also impact the uptake by inhalation. Basically, this uptake is calculated from the product of concentration in air and inhalation (Eq. (28)). Under certain conditions, such as ubiquitous background distribution of persistent compounds, we may assume that the concentrations in diet and air are near phase equilibrium. Using the formalism of Section 2.1, the equilibrium ratio K_{DA} [L kg^{-1}] between concentration in diet C_D [mg kg^{-1}] and in air C_A [mg L^{-1}] is

$$\frac{C_D}{C_A} = K_{DA} = \frac{W_D + L_D K_{OW}}{K_{AW}} \quad \left[\frac{L}{kg}\right] \tag{30}$$

where W_D is the water content [kg kg^{-1}] and L_D is the lipid content [kg kg^{-1}] of the diet.

The relation between the input data i_D (uptake of chemical with diet, mg d^{-1}) and C_D is

$$i_D = C_D F_D \tag{31}$$

where F_D is the daily dietary consumption [kg d^{-1}]. Thus, the equilibrium concentration in air $C_{A,eq}$ [mg L^{-1}] is

$$C_{A,eq} = \frac{i_D}{K_{DA} F_D} \tag{32}$$

The dose via inhalation i_A [mg d^{-1}] is subsequently

$$i_A = F_A C_{A,eq} \tag{33}$$

where F_A is the inhalation of air [mother 11 m^3 d^{-1} and child 4.5 m^3 d^{-1}].

A typical diet of an adult Danish female (F_D) contains 60 g lipids and 2 L water, hereof 1.4 L drinking water. Using these numbers, the ratio of uptake via air to uptake via diet, assuming phase equilibrium between air and food (including water), was calculated.

Fig. 5 shows that the relevance of inhalation as uptake pathway for chemicals into the human body depends much on the value of the partition coefficient air to water, K_{AW}. For non-volatile compounds (low K_{AW}, 10^{-6} L L^{-1}), inhalation is not relevant at all. With very low K_{AW} (10^{-9} L L^{-1}), the ratio of uptake with inhalation versus uptake with diet is never above 1:100,000 (not shown). On the other hand, inhalation is the dominant way of entry into the body for volatile compounds (high K_{AW}, 0.1 L L^{-1}) with up to log K_{OW} of 4. With moderate K_{AW} (10^{-3} L L^{-1} in Fig. 5), the relative importance of inhalation for the body burden decreases, but it is still higher than uptake by diet for the less lipophilic compounds (log K_{OW} ≤ 2). For lipophilic compounds (log K_{OW} > 5), which have the highest bioaccumulation, uptake by inhalation is generally not of much relevance. Compared to the mother, uptake via inhalation has similar (hydrophilic compounds) or lower importance (lipophilic compounds) for the child.

Note that these calculations were done for the rare case of near-equilibrium conditions. In real life, many individuals live in urban centers, while the agricultural production is in remote rural areas. It may be expected that the air pollution is higher in the cities, in particular when additional indoor sources of pollutants are present. Furthermore, lipophilic compounds may be strongly adsorbed to particles, which are inhaled simultaneously with air. Thus, these conclusions are surely not of general validity, and the relative importance of inhalation for the uptake of pollutants may be higher in real life than expected from the calculations displayed in Fig. 5.

4.3. Validation against empirical data

To derive their regressions for bioaccumulation in adipose tissue and breast milk, Travis et al. (1988) collected 12 bioaccumulation factors (BAFs) for human adipose tissue and six BAFs for breast milk from literature and pharmacokinetic
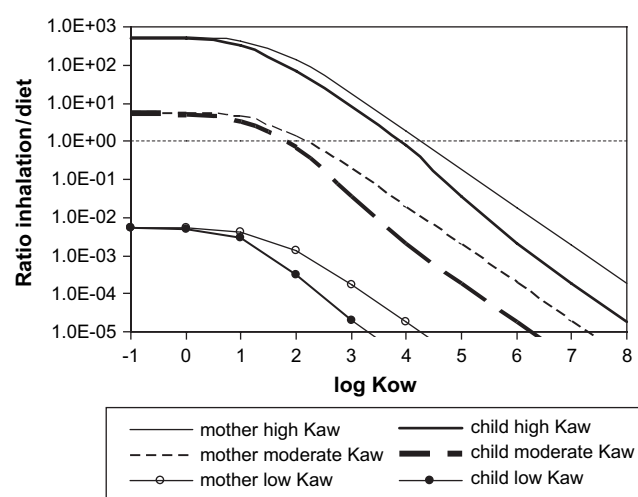
Fig. 5. Calculated ratio of uptake via inhalation to uptake via diet for the assumption of phase equilibrium for mother and child ($t = 0.5$ a) with varying log K_{OW} for high K_{AW} (0.1 L L^{-1}), moderate K_{AW} (0.001 L L^{-1}) and low K_{AW} (10^{-6} L L^{-1}). Dotted line shows ratio 1:1.

models. The model was tested against these data. Additionally, BAFs for TCDD were calculated from data in Kreuzer et al. (1997). The concentrations are related to lipid content. The log K_{OW}-values given in the original reference (Travis et al., 1988) were used, except for TCDD (Rippen, 1990–2007) (Table 2). One compound, pentachlorophenol, had to be excluded from the analysis because it is not a neutral compound but a weak acid (Rippen, 1990–2007). The uptake of weak electrolytes into living cells follows principles that are not covered by the model (Trapp, 2004).

In order to reproduce the experimental conditions under which empirical BAFs were derived, concentration in air was set to zero. Fig. 6 shows the measured BAF for human adipose tissue of the 12 organic compounds, the results from the regression by Travis et al. (1988) and the model outcome for mother before birth at steady-state. The measured BAFs range from 0.013 (TCE) to 724 (DDE) and are lowest for the volatile compounds with low log K_{OW}. Naturally, the regression predicts this range, and its results are generally less than factor 5 from the measurements, except for TCDD (over-predicted factor 21), which is out of the regression range. The model simulations are also close to the measured data and differ maximally factor 7 (dieldrin). The averaged ratio between predicted and measured BAF is 1.54 for the regression (3.15, including TCDD) and 2.0 for the model (including TCDD).

Fig. 7 shows the measured BAF for human milk of seven organic compounds. The measured BAFs range from 43 (dieldrin) to 1660 (PCB). The regression results are quite close to the measured BAF, except for TCDD. To derive the BAF, averaged values from milk samples in the period between birth and up to 18 month after birth have been used (Rogan et al., 1986). Therefore, the measured BAF were compared to the model result at birth ($t = 0$) and for $t = 1$ year. The calculated BAF milk are higher for $t = 0$ and do not vary much, as all compounds are lipophilic with log $K_{OW} > 4.7$. The predicted BAFs are somewhat too low, except for dieldrin and TCDD. The largest deviation is seen for PCB, which is not a single compound but a mix of 209 congeners. The averaged ratio between regression result and measured BAF is 2.02 (1.09
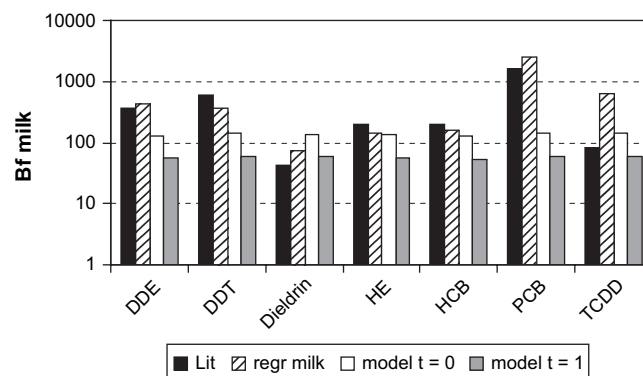

Fig. 7. Bioaccumulation factors (related to lipid content) for human milk for seven neutral organic compounds collected from literature (Lit) compared to the regression by Travis et al. (1988) and the model outcome for $t = 0$ (model $t = 0$, at birth) and $t = 1$ year (model $t = 1$).

without TCDD). The ratio between model prediction and measurements is 0.99 (0.87 without TCDD) for $t = 0$ and 0.42 (0.37 without TCDD) for $t = 1$ year.

4.4. Comment on nursing

The question is often raised whether nursing may have an adverse impact on the health of the child (BgVV, 2000). While the high dose of POPs (here: TCDD) that the infant receives with breast milk suggests so, the moderate increase of infant body concentration gives less reasons to be concerned. There is evidence that after a few life-years, the difference between breast-fed and formula-fed infants in their body burden with POPs, such as TCDD, vanishes (Kreuzer et al., 1997). If the mother nurses more than one child without longer periods in between, the model predicts lower body-burdens for the later children, i.e., for the second child after 1-year nursing, the body concentration is about the same as in the mother, if she never had breast-fed. Empirical studies confirm that the first born child is at higher risk to be exposed to POPs that have accumulated in mother and are transferred via mother milk (Tanabe and Kunisue, 2007), and that levels of POPs decrease during lactation (Harris et al., 2001). An argument pro nursing may also be that the mother reduces her POP pool (Schecter et al., 1996). Metabolism in the body of the mother reduces the dose transferred to the nursing infant. With metabolism half-times below 14 days, the model predicts that the dose the nursing infant receives is always below the dose for the mother. According to the model, the mother has a "filter effect" for less lipophilic and volatile compounds: for those, the dose for the infant via breast milk is lower than the dose mother takes up (per kg bw) (Fig. 4).

4.5. Limitations and application range of the new model

The new mother–child model is, due to the underlying equations for phase equilibrium, not valid for inorganic
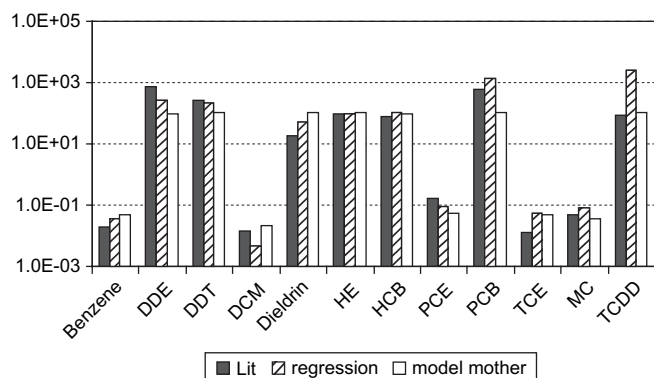

Fig. 6. Bioaccumulation factors (related to lipid content) for human adipose tissue for 12 neutral organic compounds collected from literature (Lit) compared to the regression by Travis et al. (1988) and the model outcome for mother before birth at steady-state.

(Wuenschmann et al., 2008) and electrolytic organic compounds (Trapp, 2004; Trapp and Horobin, 2005). The assumption of phase equilibrium within the body for neutral lipophilic organic compounds is supported by the results of Kreuzer et al. (1997), who found comparable levels of TCDD in lipids of adipose tissue, feces, blood, liver, breast milk and newborns. Deviations from equilibrium could in particular occur for compounds with rapid metabolism. However, for those the model predicts low transfer into infants anyhow, thus, a "false alarm" due to over-prediction would not occur, if accurate metabolism rate constants were at hand.

The new mother—child model is more complex than the regression of Travis et al. (1988), but still, the struture is easily understood, and the analytical solution of the differential equations keeps the calculations compact and robust. The model requires five chemical input parameters (i_D, K_{OW}, C_A, K_{AW} and k_{deg}). It may be more troublesome to acquire these data, but the differences in the accumulation behavior of persistent and reactive compounds can be considered, and uptake via diet and inhalation can be calculated simultaneously or separately. Therefore, results from diet studies can be used as input data, and bioaccumulation factors as defined by Travis et al. (1988) can be calculated, using $i_D = 1$ mg d^{-1} and $C_A = 0$. The regression necessarily will fail if uptake from air plays a major role.

Another advantage of the deterministic approach, compared to empirical relations, is that the relevant processes behind the BAF can be identified. The variation of physiological parameters (for the human body) allows to determine the influence of age, diet, bodyweight, growth, metabolism, etc. Furthermore, the regression violates the mass balance for more lipophilic compounds with high log K_{OW} and gives unrealistically high BAF, as was shown before.

In comparison to more sophisticated models for bioaccumulation (Kreuzer et al., 1997; Van Der Molen et al., 1996; Maruyama et al., 2003), the new mother—child model is more compact and easier adapted to new compounds (i.e., it does not require the measurement of any chemical-specific data, besides the minimum data set, and it needs no calibration steps). Compared to the human bioaccumulation model ACC (Czub and McLachlan, 2004b), which calculates the body concentration of a single human over the whole life-time, the mother—child model is less complex and more flexible, due to the analytical solution. If, for the purpose of risk assessment, only the dose for the infant is required, the differential equation system is decoupled, and the solution for the breast-feeding mother alone can be solved (Eq. (11)).

The development of the new mother—child model was driven by the need to predict the exposure of nursing children within the framework of chemical risk assessment and/or risk assessment of polluted sites. Model systems for these purposes exist (EC, 1996; Rikken et al., 2001; Kulhanek et al., 2005) but none of them considers nursing infants (in fact, children are not considered at all in most of them). The new model could be added with small effort to existing exposure assessment tools, in order to fill this gap.

4.5.1. Model availability

The new mother—child model is available as unprotected excel-spreadsheet version from the first author. Please mail to stt@env.dtu.dk.

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