Supporting Information - Part I

Assigning PBDE-concentrations to NEVO-foods

For the food categories meat, egg, milk, butter and cheese the input for the CPAP model were the PBDE concentrations expressed on a fat basis. NEVO foods belonging to these food categories were assigned the measured concentrations, expressed on a fat basis. For instance, the concentration of the NEVO food fried beef steak was calculated as the fat-based concentration of beef × fat fraction of beef steak × processing factor for frying of beef.

The input for the CPAP-model for the food categories fruit, vegetables, bread, industrial and vegetable oils, fish and crustaceans consisted of the measured PBDE-concentrations in these categories, expressed on a product basis. Vegetables (not chemically analyzed, see Table 2) were assumed to have the same concentrations as fruit. NEVO foods belonging to these ‘product-based’ categories acquire the concentrations in the corresponding categories and if relevant, a processing factor is used. For instance, the concentration of cooked cauliflower is the product-based concentration of fruit × processing factor of cooking of cauliflower.

The concentration in eel was calculated from the measured concentrations in eel by assuming that 90% of the consumption in The Netherlands consists of farmed eel, 5% of wild eel from Lake IJssel and another 5% of wild eel from other locations.

Bakery products, complex dishes and sweets were not chemically analyzed, but the concentrations in these products were entirely estimated with the measured concentrations of other categories and the CPAP-model. For example, the NEVO food chocolate spread was calculated as the fat-based concentration of milk × fraction of
milk fat in chocolate spread + product-based concentration of vegetable oil × fraction of vegetable oil in chocolate spread.

For technical reasons cheese and butter were assigned the concentration of the food category cheese or butter (on fat basis) if consumed as a separate product and when consumed as part of a complex dish (pizza) they were assigned the concentration of milk (on fat basis).
Supporting Information - Part II

Calculation of BDE-99 body burdens in animal experiments

*Kuriyama study*

5 (impaired spermatogenesis in male offspring due to prenatal, intrauterine, exposure)

Species: rat

Exposure protocol: single p.o. dose to dams at GD 6 of pregnancy

NOAEL/LOAEL: LOAEL of 60 µg BDE-99/kg.

10 Taking GD 16 as the sensitive window for the maternal body burden in the rat the remaining of the BDE-99 dose administered at GD 6 is calculated by means of a one-compartment kinetic model analysis (time: 10 days, half-life of BDE 99: 33 days (Geyer et al., 2004), fraction absorbed as for p.o. administration of 2,3,7,8-TCDD in the rat: 0.6; JECFA, 2002), or:

\[
BB_{GD_{16}, \text{rat}} = 0.6 \cdot 60 \cdot e^{\frac{\ln 2 \cdot 10}{33}} = 29.2 \ \mu\text{g/kg}
\]

(a background body burden from feed in the animal experiment is ignored).

Assuming no differences in the distribution mechanism of BDE 99 between dams and the growing embryo after single and repeated dosing this body burden is expected to lead to similar exposure of the developing embryo, whether single or repeated exposure takes place.

*Branchi study*

(neurodevelopmental toxicity in offspring due to combined prenatal transplacental and postnatal exposure via breast milk).

Species: mouse
Exposure protocol: daily, p.o., dose to dams during GD6 through PND 21

NOAEL/LOAEL: LOAEL of 600 µg/kg-bw.

Contrary to the Kuriyama study the Branchi study included a repeated dose schedule from GD 6 to PND 21.

Starting with GD6 mouse pregnancy was set to end at GD21. In this period the elimination of BDE-99 from the body was characterized by the first-order elimination constant $k_{el}$, whereas after birth elimination was augmented by lactational transfer to the offspring. After birth the elimination was characterized by the overall first order rate constant $k_{el} + k_{lac}$.

Setting the time-period between the start of the exposure, i.e. GD6, and the end of pregnancy, i.e. GD21, at $T$ and the time-period between the start of the exposure, i.e. GD6, and the end of exposure, i.e. PND21, at $T_{end}$, the time-course of the body burden $C(t)$ (µg/kg-bw) is given by:

For $t \leq T$

$$C(t) = \frac{F \cdot I}{k_{el}} (1 - e^{-k_{el}t})$$

For $t \geq T$

$$C(t) = \frac{F \cdot I}{k_{el}} (1 - e^{-k_{el}t}) \cdot e^{(k_{el} + k_{lac})(t-T)}$$

$$+ \frac{F \cdot I}{k_{el} + k_{lac}} (1 - e^{-(k_{el} + k_{lac})(t-T)})$$

With:

$F$ the fraction of the administered dose which is absorbed

$I$ the administered dose (µg/kg-bw/day)

$k_{el}$ first-order rate constant for metabolic clearance (day$^{-1}$)
$k_{lac}$  

first-order rate constant for lactational clearance (day$^{-1}$)

Over the total exposure period the average body burden can be calculated by dividing the Area Under the Curve (AUC) of the body burden by the length of the exposure period, i.e. $T_{end}$.

At $t = T_{end}$ the AUC is given by:

$$AUC = \frac{F \cdot I}{k_{el}} \left( T - \frac{1}{k_{el}} (1 - e^{-k_{el}T}) \right) + \frac{F \cdot I}{k_{el} + k_{lac}} \left(1 - e^{-k_{el}T} \right) \left( 1 - e^{-(k_{el} + k_{lac})(T_{end} - T)} \right)$$

$$+ \frac{F \cdot I}{k_{el} + k_{lac}} \left( T_{end} - T - \frac{1}{k_{el} + k_{lac}} \left(1 - e^{-(k_{el} + k_{lac})(T_{end} - T)} \right) \right)$$

The evaluation of the AUC needs values for the unknown parameters $F$, $k_{el}$, $k_{lac}$ (note that in the case of the Branchi study $I = 600 \mu g/kg-bw/day$; $T = 15$ days and $T_{end} = 36$ days).

As in the Kuriyama study the fraction absorbed was taken as for p.o. administration of 2,3,7,8-TCDD in the rat: 0.6 (JECFA, 2002). A value for the metabolic elimination rate constant was obtained by allometric scaling of its corresponding rat equivalent ($t_{1/2} = 33$ days; $k_{el, rat} = \frac{\ln 2}{t_{1/2}} = 0.021 \text{day}^{-1}$), resulting in a half-life of 18 days for the mouse ($k_{el, mouse} = 0.038 \text{ day}^{-1}$). The rate constant for lactational transfer being unknown its value was assumed to vary between equal and four times the metabolic elimination rate constant. In this way the AUC was calculated as a function of the rate constant for lactational transfer (see figure below). Finally the division of the calculated AUCs were divided by the length of the exposure period, i.e. $T_{end} = 36$ days, to obtain the average body burdens over this time period. In this way a range of
2344 to 3498 µg/kg-bw was calculated for the body burden of BDE-99 in mouse dams of the Branchi study.

The dependency of the “body burden” of BDE-99 in treated dams in the Brachi study on the rate constant for lactational transfer. X-axis: ratio of the rate constants for lactational and metabolic clearance; Y-axis: calculated body burden.

References


Safety evaluation of certain food additives and contaminants, WHO Food

exposure to low dose PBDE 99: 1. Effects on male fertility and neurobehaviour in
Supporting Information - Part III

Half-lives of PBDEs in humans

The kinetic properties of PBDEs indicate that some of these compounds have dioxinlike, bioaccumulating, properties in mammals. In the rats terminal half-lives of tetra-, penta- and hexabrominated PBDEs could directly be determined by following the decline of this compound in adipose tissue (see main text). In humans such a direct way of determining the half-life of PBDEs has only been possible for higher chlorinated PBDEs, i.e. hexa-, -hepta-, octa-, nona- and decabrominated PBDEs (see main text).

In order to obtain estimates of the half-lives of lower brominated PBDEs in humans an indirect method may be used instead, i.e. by estimating it from the “steady state” kinetics in the human body. For, assuming the long-term exposure to PBDEs to arise mainly from food (Harrad et al., 2004) and house-dust (Knoth et al., 2003; Stapleton et al., 2005; Jones-Otazo et al., 2005) such exposure may eventually result in “steady state” kinetics in the human body, i.e. a constant amount in the body. Assuming this amount to reside mainly in body fat (Staskal et al., 2005) the terminal half-life at “steady state” is:

\[ t_{1/2,\text{human}} = \frac{\ln 2 \cdot c_{\text{fat}} \cdot m_{\text{fat}}}{I_{a,f} \cdot F_{\text{abs,f}} + I_{a,d} \cdot F_{\text{abs,d}}} \]

with:
As an example the calculation of the half-life of BDE 99 is given here.

In Sweden (Geyer et al., 2004), the actual intake of BDE 99 from food was estimated in 2003 at 9.1 ng/day, with the corresponding BDE 99 concentration in body fat amounting 0.872 ng/g fat. Taking body fat masses of 13.5 resp. 18.7 kg for the average adult male and female, a fraction of BDE 99 absorbed form food of 0.89, an estimated intake from house-dust of 1.8 ng/day \(^{1}\) and an absorption fraction from house-dust ranging between zero and the absorption fraction from food, the half-life of BDE 99 may be calculated as a function of (the uncertainty in) the absorption factor from house-dust. A similar calculation may be performed for the situation in The Netherlands. For, in The Netherlands an estimate of the amount of BDE 99 in body fat may be obtained from monitoring campaigns of Dutch breast milk (2003: median concentration of 0.44 ng BDE 99 /g milk fat, body fat mass of 19.5 kg,  

\(^{1}\) For example, given a (median) concentration of 23.9 ng/g of BDE 99 in (German) house-dust (Knoth et al., 2003, Organohalogen Compounds, 61, 207 - 210) the daily intake of 50 - 100 mg dust may lead to an exposure of 1.2 – 2.4 ng/day.
Zeilmaker, unpublished results), with the actual daily intake around this time point amounting 7.7 ng/day (0.11 ng/kg-bw/day, body weight of 70 kg, this paper).

The result of this calculation, which is shown below, indicates that (1) the half-life calculation is quite insensitive for the absorption fraction from house-dust (which is not surprisingly given the relative low contribution of the exposure from house dust) and (2) that half-lives as calculated from Swedish and Dutch data are quite similar (Swedish data: max 2.8 years; min: 2.3 years; Dutch data: max: 2.4 years, min: 1.9 years).

![Graph showing half-life of BDE 99 as a function of absorption from house-dust](image)

**Figure 1.** The half-life of BDE 99 as calculated from Swedish and Dutch intake/body fat data as a function of the (assumed) absorption from house-dust.

The calculations shown in Figure 1 can also be made for BDE 47, 100, 153 and 154 (data not shown). As for BDE 99, the half-lives of these congeners, which are
summarized in Table 1, do not depend much on the absorption from house dust.

Again half-lives as calculated from Swedish and Dutch data correspond quite well, with half-lives based on Dutch data being roughly 20% lower than half-lives based on Swedish data (see Figure 2).

Table 1 Minimum and maximum estimates of the half-lives (years) of PBDEs as obtained from Swedish and Dutch intake/body fat data. Minimum estimate: $F_{\text{abs,d}} = F_{\text{abs,f}}$; Maximum estimate: $F_{\text{abs,d}} = 0$

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*as already presented in Geyer et al. (2004)
Figure 2. The correlation between half-life estimates of PBDEs as obtained from body fat/intake data in the Netherlands or Sweden. Absorption fraction from house-dust assumed to be 0.5.

References


