USING A PHARMACOKINETIC MODEL TO INTERPRET BIOMONITIORING DATA OF PBDES IN THE AUSTRALIAN POPULATION

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Introduction

From human biomonitoring data that are increasingly collected in the United States, Australia, and in other countries from large-scale field studies, we obtain snap-shots of concentration levels of various persistent organic pollutants (POPs) within a cross section of the population at different times. Not only can we observe the trends within this population with time, but we can also gain information going beyond the obvious time trends. By combining the biomonitoring data with pharmacokinetic modeling, we can re-construct the time-variant exposure to individual POPs, determine their intrinsic elimination half-lives in the human body, and predict future levels of POPs in the population.

Different approaches have been employed to extract information from human biomonitoring data. Pharmacokinetic (PK) models were combined with longitudinal data[1], with single[2] or multiple[3] average concentrations of a cross-sectional data (CSD), or finally with multiple CSD with or without empirical exposure data[4]. In the latter study, for the first time, the authors based their modeling outputs on two sets of CSD and empirical exposure data, which made it possible that their model outputs were further constrained due to the extensive body of empirical measurements.

Here we use a PK model to analyze recent levels of PBDE concentrations measured in the Australian population. In this study, we are able to base our model results on four sets[5-7] of CSD; we focus on two PBDE congeners that have been shown[3,5,8-9] to differ in intake rates and half-lives with BDE-47 being associated with high intake rates and a short half-life and BDE-153 with lower intake rates and a longer half-life. By fitting the model to PBDE levels measured in different age groups in different years, we determine the level of intake of BDE-47 and BDE-153, as well as the half-lives of these two chemicals in the Australian population.

Materials and methods

Empirical data. We used four sets of cross-sectional biomonitoring studies conducted in 2002/3, 2004/5, 2006/7, and 2008/9 in Australia[5-7]. Serum samples of more than 12'000 residents in total were collected and analyzed for PBDEs (in ng/g_{lip}). The serum samples were pooled and stratified by age and gender. The following age groups were considered for 2002/3: <16, 16-30, 31-45, 46-60, and >60 years. In the analysis from 2004/5 and 2008/2009, the age groups were: 0-4, 5-15, 16-30, 31-45, 46-60, and >60 years. Having identified that the age group of 0-4 years had accumulated higher PBDE concentrations than adults, the authors focused in their 2006/7 biomonitoring on infants and children. The age groups were the following: cord blood, 0-0.5, 0.6-1, 1.-1.5, 1.6-2, 2.1-2.5, 2.6-3, 3.1-3.5, 3.6-4, 4.1-6, 6.1-9, 9.1-12, 12.1-15, 16-30, 31-45, 46-60 and >60 years. Because the difference between genders was minimal, we used the mean concentrations of each age group to estimate the intrinsic elimination half-lives of and the level of exposure to BDE-47 and BDE-153.

PK model. We employed an adapted version of the previously described population PK model[4] that describes the changes in concentration of BDE-47 and BDE-153 as a function of age and calendar time over generations. The human body is represented as one compartment of lipids into which the chemicals distribute and which changes in volume with age[8]. The model considers an overall intake rate (in $ng/kg_{bw}/d$) that combines all different sources of PBDEs such as uptake via dust particles and diet, and it varies with age and calendar time. The PBDE intake by adults was assumed to increase exponentially from 1970 with a doubling time of 5 years, to peak in 2004, and

to decrease after 2004 with a half-life of 5 years. To derive the age-dependent intake by infants, children and teenagers from the intake function for adults, we used a proportionality factor derived from the intake estimates by Toms et al.[5]. Further, we assumed that an infant was exclusively breastfed for 6 months. All ingested PBDEs were assumed to be fully taken up. The initial concentration at birth was set equal to the mother's concentration.

Optimization procedure. We fitted the PK model to the four empirical sets of CSD by minimizing the differences between measured and modeled concentrations performing a least-square optimization[4]. In a first step, we optimized the peak intake for adults in 2004 using constant half-lives of 1.4 years for BDE-47 and 7.4 years for BDE-153[9]. These half-lives as initial starting values are also supported by Geyer et al.[2], who report 1.8 years and 6.5 years for BDE-47 and BDE-153, respectively. Next, we performed an optimization on the elimination half-lives using the peak intake from the first step, and then we continued this iterative optimization until we obtained a stable minimum for the difference between measured and modeled concentrations.

Results and discussion

Modeled CSD. Figure 1 shows the measured concentration of BDE-47 and BDE-153 together with the model results for the four cross sections through the population in 2002, 2004, 2006, and 2008. By optimizing both the half-lives as well as the peak intake rates, the model yields the best fit for half-lives of 1.1 and 2.0 years and peak intake rates of 4.0 and 1.0 ng/kg_{bw}/d for BDE-47 and BDE-153 in 2004, respectively.

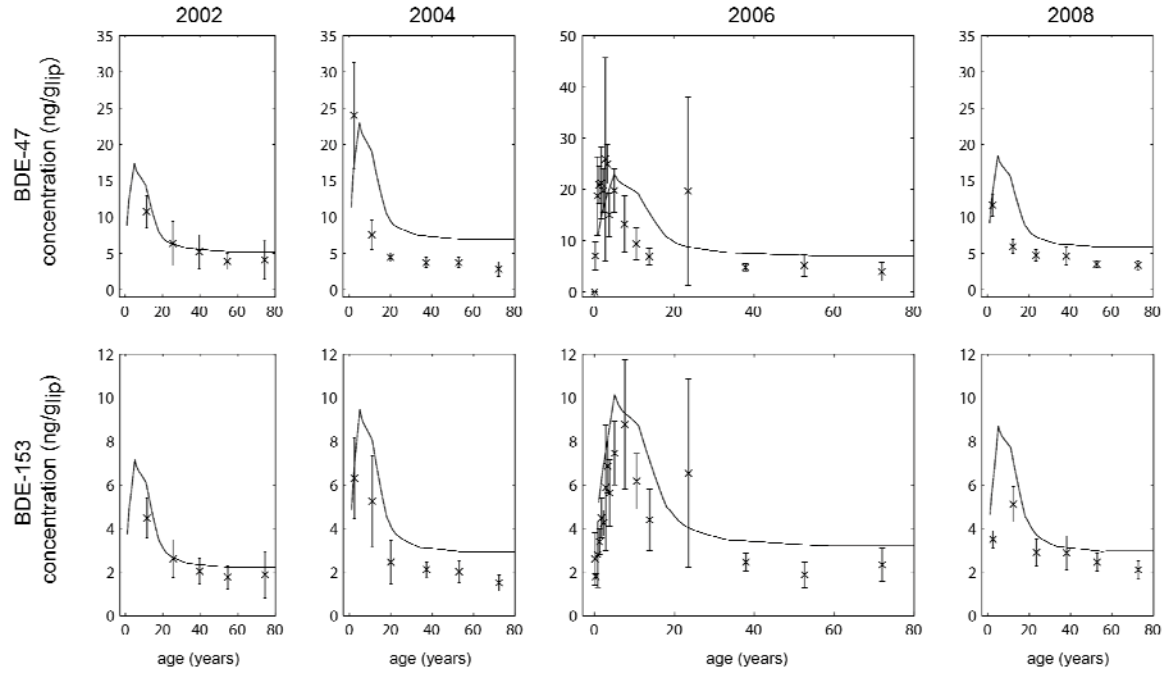

Figure 1. Measured[5-7] concentrations with standard deviation (crosses and bars) and modeled concentrations (lines) of the population cross section in four different years as a function of age and calendar year in Australia (mainly Queensland). Note the different scale in y-axis in 2006 for BDE-47.

For both congeners, the concentration peaks in children at the age of 5 and the maximum concentrations are higher in 2004 and 2006 than 2002 and 2008. This increase from 2002 to 2004 and decrease from 2006 to 2008 in the maximum concentrations is driven by the underlying intake as a function of calendar time. Both congeners have a predicted elimination half-life that is lower than the doubling time and half-life of the intake function (i.e. 1.1 years for BDE-47 and 2.0 years for BDE-153 vs. 5.0 years for the intake function). In general, the slower process (elimination or changes in intake) determines the course of the age-concentration profiles from year to

year[3]. This is the reason why the course of the intake function determines the increase and decrease in the maximum concentration.

The modeled concentrations in the adult population do not change with age; see lines for model results in Figure 1. This is caused by two assumptions made in the model: (i) all adults experience the same intake as function of time; (ii) there are no changes in the body lipid weight of adults. In contrast, the PBDE levels measured in adults show a slight decrease in Figure 1 that is not visible in the model results. Possible explanations of this trend are lower exposure of older age groups and/or increasing lipid body weight. For example, younger adults might have experienced increased exposure from their work in offices while older adults have spent less time in offices in their life. Technically, it is no problem to incorporate these effects into the model, but currently there are no empirical data available that could be used to parameterize these effects.

The measured human concentration is the result of the interplay between the chemical's elimination half-life and the intake as a function of age and calendar time. If the intake rates are high, the elimination half-life needs to be short or vice versa in order to replicate the low PBDE concentrations found in the Australian population. In our fitting procedure, we used both the peak intake rate in 2004 and the elimination half-life as adjustable parameters. This fit yielded intake rates which are by a factor of 6.3 and 14.3 higher for BDE-47 and BDE-153, respectively, compared to the intake rates estimated for the Australian population in 2004/5[5]. Toms et al.[5] calculated age-dependent and congener-specific intakes rates of BDE-47 and BDE-153 via diet, dust, and air for indoor and office environments. Our congener-specific intake rates are similar to the intake rates reported for North America[9-10], which can be interpreted as an indication that PBDE exposure in Australia and North America are on the same order of magnitude.

The half-lives obtained from our optimization procedure are shorter than reported in two other studies[2,9]. For BDE-47, our half-life of 1.1 years is only slightly lower than the best estimates of Trudel et al.[9] (1.4 years) and Geyer et al.[2] (1.8 years). For BDE-153, our estimate of 2.0 years is lower by a factor of 0.27 to 0.31 than the best estimates of Trudel et al.[9] (7.4 years) and Geyer et al.[2] (6.5 years). All these half-life estimates are clearly below the upper bound for intrinsic elimination half-life of persistent lipophilic chemicals in the human body. This upper bound is estimated at 15–20 years due to non-metabolic elimination[4,11-12]. Although half-lives of POP concentrations in humans exceeding 20 years have been reported, these high values are apparent half-lives, not intrinsic elimination half-lives[4]. This means they were derived from the time-concentration trends without accounting for ongoing exposure and/or changes in body composition. Intrinsic elimination half-lives, in contrast, describe the elimination process only, i.e. reflect the effects of metabolism and excretion, but are not affected by ongoing exposure and changes in body composition.

Outlook: Infant and child exposure and elimination half-life. For some POPs, breast milk is the main source of chemical pollutants during the postnatal phase and when the breastfeeding ceases, the concentrations in the infant decline rapidly[13]. The data in Figure 1 show a sharp increase for both congeners during the postnatal phase. Interestingly, this increase continues until the age of 5, although breastfeeding ends at the age of 6 months in our model. Due to the simultaneous physical development of the child, growth dilution would have caused a decrease in concentrations after the end of breastfeeding if breastfeeding was the only strong PBDE source. The prolonged increase in PBDE concentrations indicates that other sources in addition to breast milk lead to significant PBDE intake. It has already been hypothesized that infant- and child-specific behavior such as mouthing and suckling products that causes increased uptake of contaminated soil, dust, and leachates from PBDE-containing products might be the missing source[5-6].

Additionally, studies on infant exposure to TCDD[10-11] and DDT[13-14] have shown that infants have shorter intrinsic elimination half-lives of POPs than adults, because fecal lipid excretion is higher at younger ages. In the present modeling exercise, we have not yet considered this effect. If an age-dependent half-life of individual PBDE congeners is assumed, the higher excretion by infants and children will have to be compensated for by even higher intake rates for the model to match the levels of PBDEs found in the Australian children.

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