IS THERE AN UNKNOWN EXPOSURE PATHWAY FOR PBDEs? EVIDENCE FROM NORTH AMERICAN BIOMONITORING DATA

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Introduction

Polybrominated diphenyl ethers (PBDEs) are the most studied flame retardants over the past two decades in human exposure assessments, but their pharmacokinetics in the human body are not well characterized. Estimates of elimination half-lives for PBDEs in humans have been extrapolated from a rat study [1], and calculated from a longitudinal study in which the changes in PBDE levels of occupationally exposed individuals were followed [2]. Others have combined biomonitoring and exposure studies to estimate the elimination half-lives using a steady state pharmacokinetic (PK) model [1, 3]. These half-life estimates differ by factors of 2 to 7. Studies which have applied these half-lives in PK models to calculate body burdens or intake have indicated that the current half-life estimates are not consistent with exposure estimates [4-6]. This may be a result of uncertainty in the elimination half-lives, or in the exposure estimates.

Recently, a population-level PK model was developed to estimate intrinsic elimination half-lives from biomonitoring and exposure data, and was demonstrated for polychlorinated biphenyls in the UK population [7]. The model defines the relationship between exposure, biomonitoring and elimination of a chemical from an individual as,

$$\frac{\partial C(t)}{\partial t} = I(t) - k_e \cdot C(t) \quad (1)$$

where $C(t)$, ng/g lipid, is the lipid-normalized concentration of a chemical in the body as function of time, $I(t)$, ng/kg body weight/day, is the intake from all external exposure pathways (assuming 100% absorption), and k_e, year^{-1}, is the intrinsic elimination rate constant from the human body. The model treats representative humans in the population as single, well-mixed compartments for chemicals. k_e is chemical specific, but is assumed to be the same for all members of the population and for all intakes. Eq (1) is solved for k_e using empirical biomonitoring and total exposure pathway datasets. In the UK case study for PCBs, the biomonitoring and exposure data are consistent, and k_e could be derived solely from biomonitoring studies [7].

The goal of this modeling study is to rationalize the estimates of human elimination half-lives with empirical biomonitoring and exposure studies for the North American population. The population-level PK model from Ritter et al. [7] is used to evaluate the consistency between PBDE biomonitoring and exposure datasets. This is achieved by i) fitting intrinsic elimination half-lives to multiple sets of biomonitoring and exposure data in different combinations, and ii) comparing the modeled intake and intrinsic elimination rate constants and those obtained from other studies.

Materials and methods

Biomonitoring data Eight distinct biomonitoring datasets that reported PBDE levels in serum or breast milk in the general population of North America were collected. These studies were conducted during 1992 to 2009. In our data analysis we assume that lipid normalized PBDE concentrations in serum and milk are comparable, which would be the case if the lipid compartments in the body are in equilibrium, which is consistent with the assumption made for PCBs by Ritter et al [7].

Exposure data Congener specific daily intake for the North America population has been estimated in two total exposure studies [3, 5]. Exposure pathways from these studies include ingestion of food, dust/soil, inhalation of air and dermal contact of dust/soil, and organic film. Estimates from Trudel et al. [3] are derived

from exposure studies conducted during 2001 to 2010, while those from Lorber [5] are from studies conducted from 2002 to 2006. These estimates are assumed to represent intakes in 2005 and 2004 respectively.

The PK model The population-level PK model is described by Eq (1) and detailed in ref [7]. The concentration of chemicals in the human body as function of age and calendar time is modeled while accounting for changes in body weight and ongoing exposure. The estimated exposure intake considers all known exposure pathways. We assume that the intake of PBDEs began in 1970, increased exponentially and peaked in 2004. We fit the model to empirical exposure and biomonitoring data using the weighted least-square (*SSRW*) optimization method. *SSRW* for the biomonitoring ($SSRW_{Bio}$) and exposure intake ($SSRW_{Intake}$) are calculated and expressed as an objective function (*OF*). The model is fitted to the empirical biomonitoring and intake (OF_{Bio_Intake}, eq. 2) and biomonitoring datasets only (OF_{Bio}, eq. 3). Each objective function gives point estimates of the intake (ng/kg bw/day) in 2004 and 2038, and the intrinsic elimination rate constant (k_e, year^{-1}). The intrinsic elimination half-life ($t_{1/2}$, years) is calculated as $\ln(2)/k_e$.

$$OF_{Bio\_Intake} = SSRW_{Bio} + SSRW_{Intake} \quad (2)$$

$$OF_{Bio} = SSRW_{Bio} \quad (3)$$

In cases where the intrinsic half-lives ($t_{1/2}$) calculate from OF_{Bio_Intake} and OF_{Bio} do not agree, OF_{Bio} is run by constraining intakes that would give $t_{1/2}$ <15 years and this is referred to as OF'_{Bio}. Boundaries for $t_{1/2}$ are set on the basis that the maximum elimination half-live of organic chemicals, such as PCBs and dioxins should not be greater than 15 years due to non-metabolic clearance processes [8, 9]. The model is run for BDE-47, -99, -100 and -153.

Results and discussion

Fitting the model with OF_{Bio_Intake} results in infinite intrinsic half-lives for all PBDE congeners. This result suggests that even if there is no clearance of the chemical from the body during the lifetime of an individual, it is impossible for one to accumulate the observed level base on the current empirical exposure intake estimates. When the model is fitted with OF_{Bio}, estimated intrinsic half-lives (years) are; for BDE-47 = 0.37, BDE-99 = 8.3, BDE-100 = 1.3 and BDE-153 = 2.7, and the intake values are up to 2 orders of magnitude higher than the literature values. The strongly divergent results generated from OF_{Bio_Intake} and OF_{Bio} imply that an actual discrepancy between the measurements gathered from exposure and biomonitoring studies exists.

Combinations of half-lives and exposure that are consistent with the biomonitoring data are identified by fitting the model OF'_{Bio} by constraining intake values that would give $t_{1/2}$<15 years. Each intake scenario corresponds to one optimized $t_{1/2}$ that would provide the best fit to the empirical data. Figure 1 illustrates the modeled and empirical data for BDE-47 in three dimensions assuming $I(2004)$ = 8 ng/kg bw/day and $t_{1/2}$= 3.6 years. In Figure 1, the top left panel shows intake as a function of time. It shows that the assumed intake in 2004 is greater than the empirical estimate. The top right panel presents the modeled lifetime chemical body concentration as function of an individual's year of birth. At age 0 to 4, body concentration rises rapidly as result of breast milk consumption for infants and increased exposure to dust for toddlers. Concentration then declines at age 4 due to the effect of growth dilution and the assumed reduced exposure to dust. The body concentration decreases slowly as an individual grows. The bottom panel is the body concentration as function of age at a specific sampling year. The modeled and empirical chemical body concentration is shown. It indicates that children had elevated levels of BDE-47 compared to adults in all sampling years.

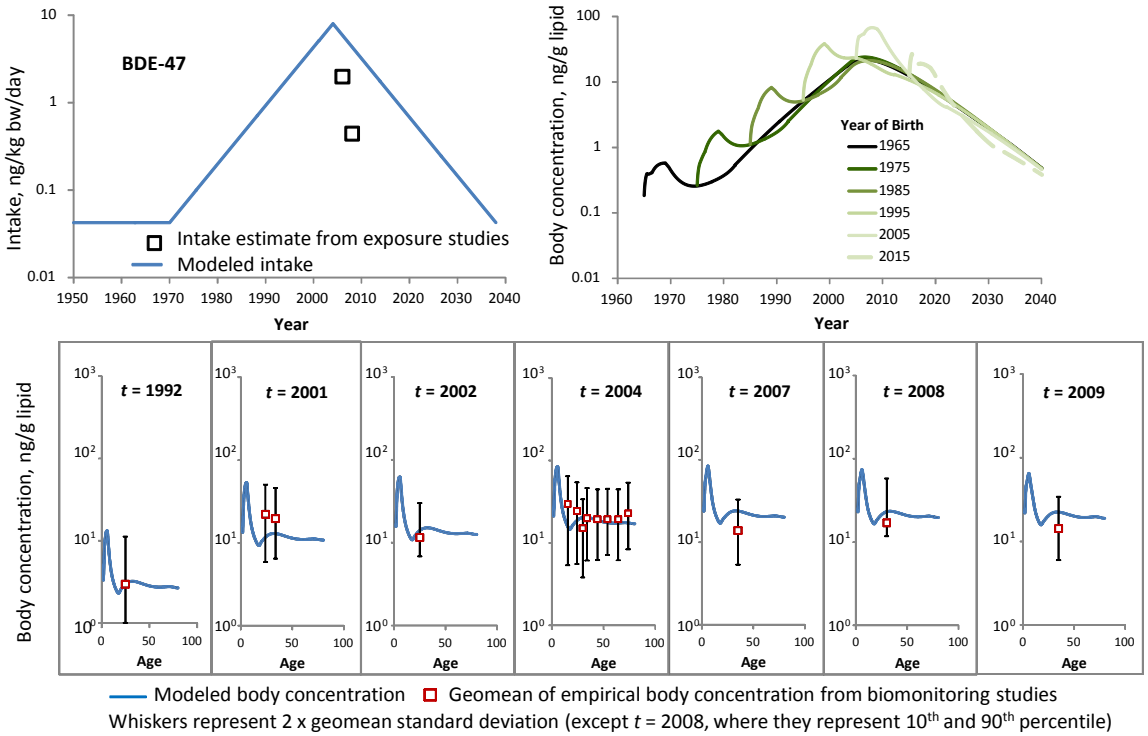

Figure 1. Empirical and modeled data for BDE-47 in the North American population using OF'_{Bio}, assuming intake in 2004 was 8 ng/kg bw/day and an intrinsic elimination half-life of 3.6 years. Top left: Intake as a function of time, $I(t)$. Top right: Body concentration for individuals born in different years. Bottom: Body concentration as function of age in a specific sampling year.

Table 1 shows the literature and modeled intake and elimination half-life estimates. We calculate intakes using the biomonitoring data and elimination half-lives extrapolated to humans from a rat study [1], the modeled intake for BDE-47 and -153 are 9.5 and 1.2 ng/kg bw/day respectively. These are a factor of 5 higher than the empirical estimates for BDE-47 and -153 by Lorber [5]. Even when we assume the maximum plausible elimination half-life of 15 years, intakes are still 2 and 5 times greater than empirical estimates for BDE-47 and -153 respectively. These intakes represent the plausible minimum that is required to explain the biomonitoring data.

Table 1. Literature and modeled exposure intakes and human elimination half-lives of PBDE.

Data type/studies	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**
Intakes from total exposure pathway studies (ng/kg bw/day)				
Trudel et al., 2011 (North America, Mean) [3]	0.44	0.48	0.19	0.051
Lorber, 2008 [5]	1.98	2.19	0.83	0.23
This study, assuming $t_{1/2}$ from a rat study, Geyer et al.,[1]	9.5	1.72	2.08	1.27
This study, assuming maximum plausible $t_{1/2}$ of 15 years	3.9	0.93	0.98	1.14
Human elimination half-lives (years)				
Geyer et al., 2004 (rat study) [1]	3	5.4	2.9	11.7
Geyer et al., 2004 [1]	1.8	2.9	1.6	6.5
Trudel et al., 2011 [3]	1.4	0.77	1.8	7.4

Our results point to the inconsistencies between the exposure and biomonitoring data. The inconsistency could be due to 1) underestimation of exposure of the North American population to PBDEs, 2) underestimation of the half-lives for clearance of PBDEs from humans, or a combination of the two. Similar inconsistencies have been reported in other studies from industrialized countries. Toms et al. [4] used a steady-state PK model to explain their empirical data obtained from the Australian population and reported that their model under-predicted the empirical values. In that exercise, half-lives derived from human biomonitoring data from Sweden were employed [1]. The authors suggested that either additional exposure pathways other than consumption of breast milk and food, air inhalation and dust ingestion contribute to the human body burden or that the half-lives may have been underestimated. Lorber [5] carried out a forward PK modeling to calculate the body concentration of PBDE in the general background-exposed American human population based on exposure intake estimates. This was done by using a steady-state PK model which used half-lives extrapolated from a rat study [1]. He found that the PK model under-predicts the empirical body concentration for BDE-47 in serum by at least 4 times. Again, the authors speculated that the half-life of BDE-47 was underestimated.

Literature on exposure pathways of PBDE is abundant for the North American population, with most studies focused on one specific pathway. However, assessment of total exposure and time trends is limited. Uncertainty associated with PBDE exposure to house dust, in terms of its intake rate, concentration, and bioavailability is high. Debromination of higher to lower brominated congeners can be an additional exposure pathway which has been previously observed in animal studies [10]. However, studies have not been undertaken to determine the relevance of this pathway for humans. Only one of our datasets contains age-stratified data. The availability of additional age-stratified datasets would better constrain the model and compensate for the scarcity of reliable exposure data.

Although we are currently unable to provide accurate estimates of human elimination half-lives for PBDEs based on the available exposure and biomonitoring data, we have been able to define the boundaries of possible exposure intakes which can explain the North American human biomonitoring data. Comparison of the modeled exposure intakes with those previously estimated from empirical data [3,5] as well as comparison of the range of half-lives used in the PK model with our understanding of PBDE elimination kinetics, indicates that total external exposure intake may have previously been underestimated in North America.

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