PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING AS A TOOL FOR PREDICTING LIFETIME EXPOSURE OF PBDE IN HUMANS: FROM INFANTS TO ELDERLY.

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Introduction

Polybrominated diphenyl ethers (PBDE) are brominated flame retardants (BFRs) which have been produced since the 1970s and are used in a variety of flammable consumer products such as electronics, plastics, textiles, and foam padding[1]. PBDEs migrate from these products and thus potentially expose humans. There are 209 PBDE congeners, but the major ones found in the environment are BDE-47, -99, -100, -153, -154, and -209. PBDEs are very stable in the environment and are known to settle in particles and sludge. The combination of high lipophilicity, low volatility, and low elimination rates gives these chemicals a relatively high potential for bioconcentration and biomagnification. PBDEs have been detected in various tissue samples in different species including humans [2,3,4,5]. The major congener found in most biota is BDE-47.

Children, infants and fetuses are thought to be more sensitive to the health effects of environmental pollutants, particularly for non-cancer effects because they are undergoing critical developmental processes [6]. In addition, altered sensitivity of developing organisms may be due to specific life stage differences in the pharmacokinetics of xenobiotics. Pharmacokinetics encompasses information on the absorption, distribution, metabolism and elimination (ADME) of a chemical in biological systems. Our hypothesis is that many diseases appearing in adults are due to exposure early in life during sensitive periods and progress slowly until the symptoms and disease ultimately appears. It is well documented in the literature that PBDEs are transferred to the foetus and from mother to child via milk during nursing[7]. The development of physiologically-based pharmacokinetic models (PBPK) may provide insight into the pharmacokinetic differences during various life stages. We have developed PBPK models describing the behavior of BDE47 in mice and rats [8,9]. To our knowledge, PBPK models that examine lifetime exposure to PBDEs in humans have not been described.

The objective of this project was to use a PBPK model to characterize the influence of age-specific physiological parameters on the body burden during lifetime exposure to PBDEs.

Methods and Materials

Model development, Parameterization and Validation:

In the present project, a PBPK model has been developed to describe the ADME for BDE-47 in women during their lifetime (Figure 1). This PBPK model contains 4 compartments: brain; liver; adipose tissue; and rest of the body. Distribution of BDE-47 to the adipose and brain compartments was described as a diffusion-limited process, while to the liver and rest of the body compartments, distribution was described as a flow limited process. The compartments are connected through systemic circulation. Model parameters (i.e. tissue volumes, cardiac output, blood flow to tissues, partition coefficients, diffusion constants, and elimination constants) were obtained from the literature[10,11].

Growth of the tissue compartments such as brain, liver, adipose tissue and blood flow were described with polynomial equations which were adapted from experimental data found in the literature[12,13]. Partition coefficients were described with the equation developed by Poulin[14]. The elimination of BDE-47 was described with an extraction coefficient equation as follows:

$$RAM = C_{BDE47} \times Ql \times E$$

where:

RAM = Rate of elimination from liver compartment (ng/hr)
CB_{DE47} = Blood concentration in BDE-47 (ng/ml)
E = Extraction coefficient (unitless)
Ql = Liver blood flow (ml/hr)

The algebraic and differential equations describing the kinetics of BDE-47 were solved with commercially available software (ACSL® Advanced Continuous Simulation Language, AEGIS Technologies Group, Inc., Huntsville, AL)

Data from the literature were used to analyze the behavior of the PBPK model. Schecter et al. (2007) measured different PBDE congeners in fetal liver and blood of the mother[7]. The minimum and maximum concentration was reported to be 4 and 365 ng PBDEs/g lipid, respectively, in the women's blood lipids, of which about 48% is BDE-47. Thus, in our modeling exercises, we will assume a high and low blood concentration of 1.92 and 175.2 ng BDE47/g lipid. Simulations were performed to predict the exposure that will result in both of these concentrations. In other words, we will use the model to back calculate a dose that predicts these tissue concentrations, and further, since Schecter et al. (2007) studied women of child-bearing age, we will assume these concentrations are characteristic of a woman who is 25 years old. The age range used in the simulations to evaluate the impact of exposure during the lifetime was from 0 to 80 years old**.** The extraction coefficient (E) was varied between 0.00 (representing maximum risk) and 0.005, which represents the same range observed with other POPs. The final results of this exercise are shown in Figures 2 and 3, which show the range of body burdens over a lifetime and doses required to achieve a 1.93 ng/g lipid in a 25 year-old (Figure 2) and a 175.2 ng/g BDE47/g lipid in a 25 year-old (Figure 3).

Results and Discussion

Simulation of lifetime exposure with a physiologically based pharmacokinetic model provides information about the profiles of exposure for a chemical such as BDE-47 during a specific life stage. A PBPK model can also describe the body burden or target tissue concentration during windows of sensitivity. One difficulty of conducting a lifetime simulation is to describe the exposure conditions over a lifetime. This is easier when people live at the same place for their entire lives and work at the same place. An intense evaluation of exposure characterization needs to be pursued. For the development of this PBPK model, emphasis was placed on the description of each organ. We described the variation of the tissue volume and perfusion as a function of age in each compartment. Because the percentage of body fat and liver mass varies with age, this affects the disposition of chemicals such as persistent organic pollutants (POPs). This is particularly true because of the increase in obesity of people in industrial countries.

When E = 0.00, no elimination occurs and maximal accumulation is reached for low background exposure dose. However, when the extraction coefficient E=0.005 a higher background exposure dose is needed to reach the observed blood concentrations. The lifetime profile is helpful because it takes into account the variability in physiology and anatomy of women and the history of exposure to the chemical. For example, adult women having the same blood concentration today were not necessarily exposed at the same exposure level in the past. Thus, an effect observed in one woman can be explained by the establishment of her exposure profile which may not reflect the exposure profile of another.

This development of a PBPK model provides a powerful tool for risk assessment as well as for understanding basic pharmacokinetic and pharmacodynamic processes during lifetime exposures. During life, women go through different critical stages (birth, puberty, and menopause) during which important physiological and biochemical processes occur. Understanding the relationship between these critical stages and dose metric parameters are important determinants in understanding the latency of disease, the clinical signs of which may appear many years after the exposure. This important modeling work has several implications for humans. In humans, the average body fat mass is estimated to be approximately 25% and is much higher in obese populations. A low or high background exposure in obese populations will have a different impact than in lean populations. The influence of variation in the body fat mass would allow for a better understanding of the pharmacokinetics of exposure to background levels of PBDEs in human populations.

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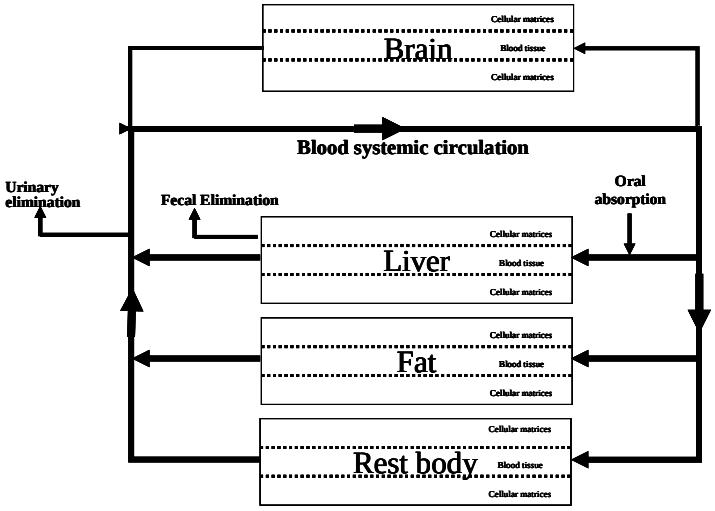

Figure 1: Conceptual representation of lifetime PBPK model for human.

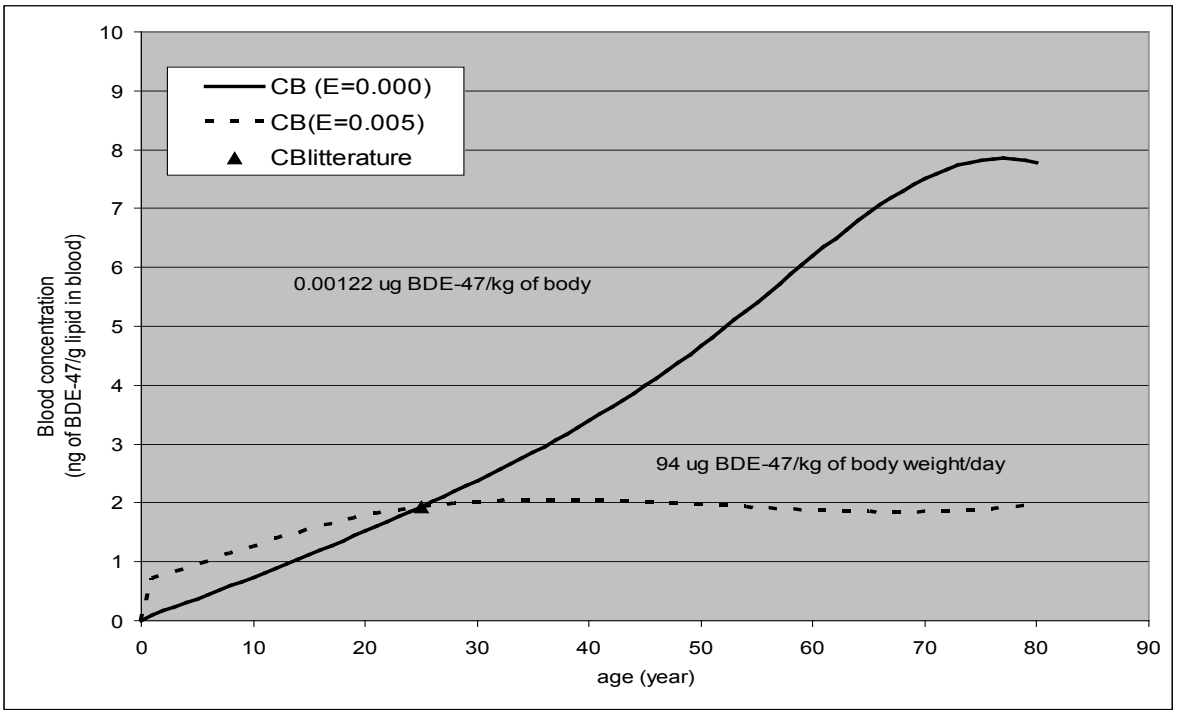

Figure 2: Blood concentration during lifetime exposure at 0.00122 ug of BDE-47/kg of body weight /day for a (E= 0.000 (dotted line)) and 94 ug of BDE-47/kg of body weight/day for a (E= 0.005 (dotted line)) resulting in an average blood concentration of 1.93 ng/g lipid in blood in for a 25 year old woman

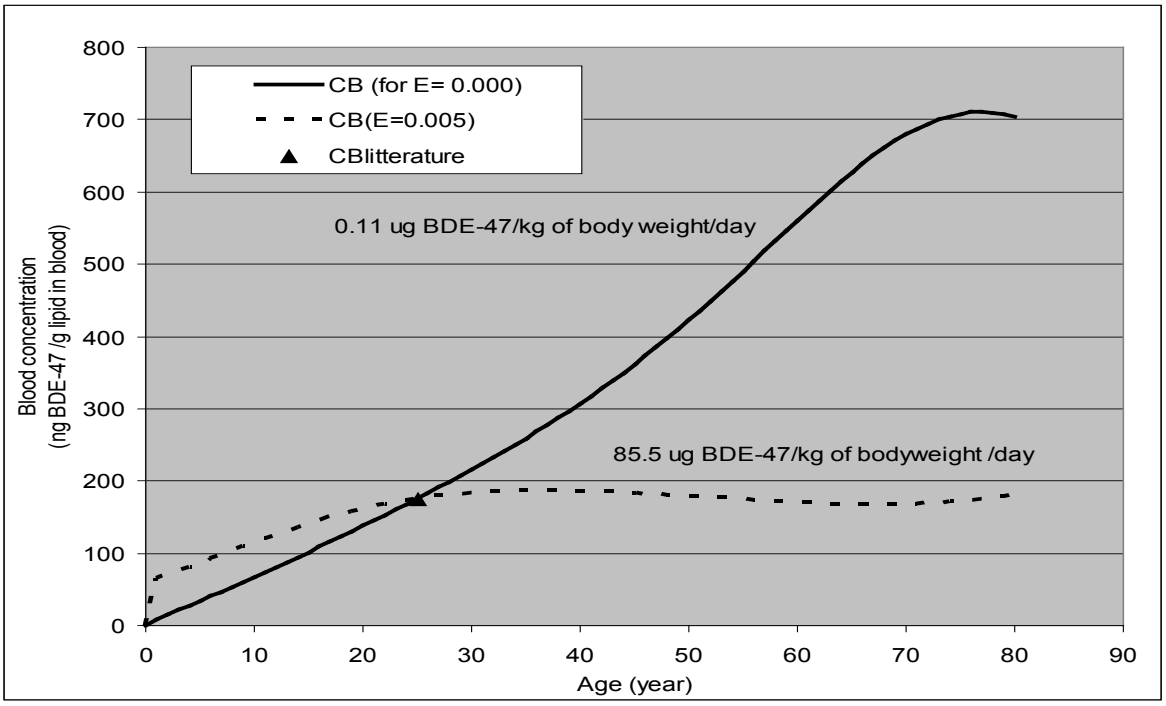

Figure 3: Blood concentration of BDE-47 during lifetime exposure at 0.11 ug of BDE-47/kg of body weight /day for a (E= 0.000 (dotted line)) and 85.5 ug of BDE-47/kg of body weight/ day for (E= 0.005 (full line)) resulting in an average blood concentration of 175.2 ng of BDE-47/g lipid in blood for a 25 year old woman.

References

1. Fangstrom, B., Athanassiadis, I., Odsjo, T., Noren, K., and Bergman, A. (2008). Mol Nutr. Food Res 52(2), 187-193.2)- Harrad, S., and Porter, L. (2007). Chemosphere 66(10), 2019-2023.
2. Sjodin, A., Wong, L. Y., Jones, R. S., Park, A., Zhang, Y., Hodge, C., DiPietro, E., McClure, C., Turner, W., Needham, L. L., and Patterson, D. G., Jr. (2008). *Environ Sci Technol* **42**(4), 1377-1384.
3. Toms, L. M., Harden, F. A., Symons, R. K., Burniston, D., Furst, P., and Muller, J. F. (2007).. Chemosphere 68(5), 797-803.
4. Birnbaum, L. S., and Staskal, D. F. (2004). Environ Health Perspect. 112(1), 9-17.
5. Akutsu, K., Kitagawa, M., Nakazawa, H., Makino, T., Iwazaki, K., Oda, H., and Hori, S. (2003).. Chemosphere 53(6), 645-654.
6. Daston, G., Faustman, E., Ginsberg, G., Fenner-Crisp, P., Olin, S., Sonawane, B., Bruckner, J., Breslin, W., and McLaughlin, T. J. (2004).. Environ Health Perspect 112(2), 238-56.
7. Schecter, A., Johnson-Welch, S., Tung, K. C., Harris, T. R., Papke, O., and Rosen, R. (2007). J Toxicol Environ Health A 70(1), 1-6.
8. Emond, C., DeVito, M., and Birnbaum, L. S. SOT. Society of toxicology. 42th annual meeting and ToxExpo . 2003. Salt Lake city, SOT.
9. Emond C. Stastkal D.F . Birnbaum L.S, (2007) Dioxin 2007, 27th International Symposium on Halogenated Persistent Organic Pollutants, Tokyo, Japan
10. Krishnan, K. (2007). (A.W.Hayes, Ed.), 5th ed., pp. 231-291. CRC Press, New York.
11. Emond C., Staskal, D. Birnbaum L.S. (2007) IX International Congress of Toxicology, Montreal, Quebec, Canada
12. Luecke, R. H., Pearce, B. A., Wosilait, W. D., Slikker, W., and Young, J. F. (2007).. Journal of Toxicol and Environ. Health, Part A 70(12), 1027-1037.
13. Pelekis, M., Nicolich, M. J., and Gauthier, J. S. (2003). Risk Anal 23(6), 1239-1255.
14. Poulin, P. and Krishnan, K. (1996). Toxicol.. Methods 6(3), 117-137.