INTRINSIC SERUM ELIMINATION HALF-LIVES OF TRI- TO HEXABROMINATED DIPHENYL ETHERS: DETERMINED IN PERSONS MOVING FROM NORTH AAMERICA TO AUSTRALIA

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Introduction

Directly measured serum polybrominated diphenyl ethers (PBDE) elimination half-lives from subjects transiting from a high to a low exposure situation has been missing in the literature except in the case of the relatively short lived congeners from a study of e-waste recyclers being exposed occupationally to technical Octa- and DecaBDE. The decline in these workers serum concentration was measured before and after their summer vacation spanning approximately four weeks; the half-lives of BDE183 and BDE209 were reported to be 3 months and 2 weeks[1], respectively. Other studies include estimates of half-lives from dietary intake with the assumption of steady state concentration or extrapolation from determined half-lives in the rat[2], and a population level pharmacokinetic model.[3]

Our objectives were to estimate the intrinsic serum elimination half-life of tri- to hexaBDEs in North American subjects moving to Brisbane, Australia, which is a lower exposure region for PBDEs than their country of origin.

Materials and methods

Subjects: We recruited participants among persons moving from North America (Canada and the United States) to Brisbane, Australia and persons living in the general area of the city of Brisbane from March 2011 to June 2013. Recruitment was through advertisement at local Universities in Queensland (Queensland University of Technology and The University of Queensland) as well as word of mouth. Inclusion criteria were that the subjects must have lived in the same general location (city and/or state) in their country of origin for at least 5 years and planning to remain in Brisbane, Australia for a minimum of 6 months.

We obtained ethics approvals from Queensland University of Technology Ethics Committee and The University of Queensland Ethics committee. The Centers for Disease Control and Prevention (CDC) laboratory was determined not to be engaged in human subjects' research; no personally identifiable information was made available to CDC researchers.

The inclusion criteria for deriving an elimination half-life of PBDEs for a subject were having (i) four or more serum samples collected, (ii) an initial serum concentration at least three-fold the average serum concentration in Australia (Figure 1) with concentrations below the LOD set to zero, and (iii) a sample collection period of more than one year corresponding to the approximate half-life of most PBDE congeners investigated except BDE153. Unfortunately, only one North American subject met the inclusion criteria. That subject had a total of 6 serum draws during a period of 1.5 years and an initial BDE47 concentration of 34.1 ng/g serum lipid (Figure 1).

Measurement of PBDEs in serum: Serum PBDE concentrations were measured using established methods at the CDC.[4, 5]

Statistical Approach: The decline in PBDE serum concentration was assumed to follow Equation 1 as presented in Russell et al. [6] where: t is the time in days passed since the collection of the initial serum sample after arriving in Australia; $C_{Australia}$ is the steady state concentration for a subject living in Australia; C_0 is the subject's initial serum concentration (initial serum sample collected at t=0) and k_e is the intrinsic elimination constant that is related to the intrinsic elimination half-life by Equation 2.

$$\textbf{Equation 1:} \quad C(t) = C_{Australia} + (C_0 - C_{Australia})e^{-k_e t}$$

$$\textbf{Equation 2:} \quad t_{1/2} = {\ln(2)}/{k_e}$$

Due to the fact that only one subject was determined to fulfill all inclusion criteria for calculation of elimination half-life, we decided to use a Monte Carlo[7] simulation approach to estimate the uncertainty in the derived

elimination half-lives. The simulation was conducted in SAS Enterprise Guide 7.1 (Cary, NC). In the simulation, the variable $C_{Australia}$ was defined as a random generated number from the natural logarithm distribution derived from the Australian subjects (weighted by the number of samples collected by participant) with concentrations below the LOD set to the LOD divided by the square root of two. Each measured concentration was in the simulation multiplied with random number from a Gaussian distribution with a mean of 1.00 and a standard deviation of 0.05 corresponding to the analytical uncertainty of the measurement, i.e., CV of 5%.
The SAS program iteratively determined the optimum fit for k_e by analyte for 10,000 random generated values of $C_{Australia}$ including random generated analytical measurement uncertainty for each measured concentration.

Results and discussion:
Twenty-three Australians and twenty-seven North Americans participated in the study. The median concentration of PBDEs were 3.5 [BDE153] – 16 [BDE47] fold higher in North American than in Australian subjects. North American subjects followed during their stay in Brisbane, Australia had a decreasing concentration as measured during their stay while Australian subjects varied in a non-consistent direction during the study period (data not shown). The subject meeting the inclusion criteria for deriving an elimination half-life had a serum concentrations that were 3.5 [BDE153] to 16 [BDE47] fold higher than the average Australian concentration. Concentrations over time for this subject that who was followed for 1.5 years and is are given in Figure 1 for BDE47. The median Monte Carlo derived half-life with 2.5th and 97.5th percentile ranges and model parameters are given in Table 1.

Intrinsic elimination half-life estimates unaffected or adjusted, as in our case, for ongoing exposures through food, dust ingestion and/or other sources of exposure are an important parameter to study. They are especially needed to assess the effect of regulations intended to decrease and/or eliminate a population's exposure to a pollutant such as PBDEs. In the United States, the National Health and Nutrition Examination Survey (NHANES) investigates trends in serum concentrations of pollutants over years and even decades as in the case of PBDEs, lead and other pollutants of concern. Technical Penta- and OctaBDE were voluntarily withdrawn from the United States market in 2004 and has have since then been included in pooled measurements in five biannual surveys covering the time period 2005/06 through 2013/14. In the case of BDE47, the serum concentration dominating congener has decreased by 49%, 53%, 19% and 45% in 12-19, 20-39, 40-59 and subjects over the age of 60 years, respectively. Considering that this period spans multiple half-lives we can conclude that elimination from the Unites States market has decreased exposure, but not eliminated it.

Limitations: The limitations of this investigation include lack of subjects with a sufficiently long study period caused by subjects being exchange students or workers mostly limited to one semester in Australia. Due to this, we were limited to using one subject with a long sampling period of 1.5 years who also had an unusually high initial PBDE serum concentration corresponding to between the 75th and 90th percentile of NHANES 2003/04. Other limitations include limited length of time studied especially for BDE153 where only 40% of one half-life were sampled. This short sampling period decreased the precision of the estimate but it is clear that BDE153 has a half-life that is longer than the other tri- to pentaBDE congeners investigated here. Furthermore, all tri- to hexaBDEs investigated here has have much longer biological half-lives than BDE183 and BDE209 which are measured in months to weeks.

Table 1. Serum half-life of polybrominated diphenyl ethers based on one subject with 6 repeated serum measurements spanning over 547 days from a total of 10,000 iterations with median and range of model parameters indicated.

Congener	Half-life (Years)		Model Parameters [Median (range)] [1]		
	Median	(P2.5 - P97.5)	C_0 [2]	$C_{australia}$ [3]	k_e [3]
BDE28	0.942	(0.803 - 1.04)	2.30 (1.88 - 2.77)	0.407 (0.224 - 0.848)	0.00202 (0.00174 - 0.00331)
BDE47	1.19	(1.08 - 1.25)	34.1 (26.1 - 42.1)	2.136 (0.615 - 7.02)	0.00160 (0.00148 - 0.0021)
BDE99	1.03	(0.845 - 1.15)	6.01 (0.629 - 0.968)	0.916 (0.345 - 2.64)	0.00184 (0.00157 - 0.00394)
BDE100	2.16	(2.01 - 2.25)	9.18 (4.75 - 7.2)	0.679 (0.274 - 1.74)	0.000881 (0.000811 - 0.00105)
BDE153	4.12	(3 - 4.84)	7.10 (5.6 - 8.72)	2.016 (0.741 - 5.16)	0.000461 (0.000362 - 0.00157)

[1] Detailed definition of model parameters is given under heading "Statistical Approach". [2] Initial concentration of North American subject (ng/g lipid). [3] Background concentration (ng/g lipid). [4] Elimination rate constant.

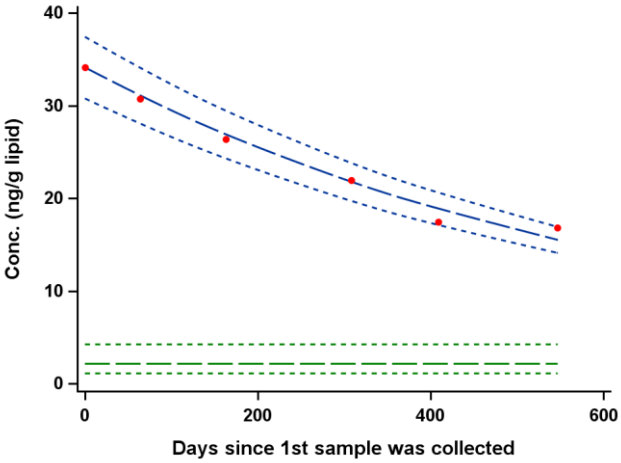

Figure 1. Elimination of BDE47 with resident time (1.5 years) in Australia for the single subject selected for half-life determination. Red dots shows actual measured concentration and blue lines shows median concentration and 2.5th and 97.5th percentiles of concentration estimates from 10,000 iterations (see Materials and methods for underlying assumptions). Green lines shows median and 2.5th and 97.5th percentiles of the Australian subjects.

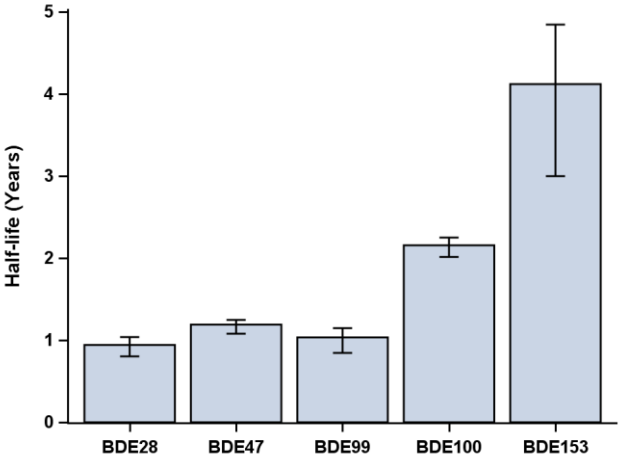

Figure 2. Median estimate of intrinsic elimination half-life for tri- to hexaBDE congeners. Error bars indicates 2.5th and 97.5th percentile of Monte Carlo estimate.

References:

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