Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans

Harald J. Geyer[1], Karl-Werner Schramm[1], Per Ola Darnerud[2], Marie Aune[2], Ernst Anton Feicht[1], Kristian W. Fried[1], Bernhard Henkelmann[1], Dieter Lenoir[1], Peter Schmid[3], Thomas A. McDonald[4]

[1]GSF-National Research Center, Institute of Ecological Chemistry, Neuherberg, Germany
[2]Swedish National Food Administration, Uppsala, Sweden
[3]Swiss Federal Laboratories for Materials Testing and Research, Laboratory of Organic Chemistry, EMPA Duebendorf, Duebendorf, Switzerland
[4]Office of Environmental Health Assessment, California EPA, Oakland, USA

Introduction

Brominated flame retardants (BFRs) are widely used in polymers and textiles and applied in electronic equipment, construction materials, and furniture for the purpose of fire prevention. BFRs with the highest production volume are tetrabromobisphenol A (TBBPA), 1,2,5,6,9,10-hexabromocyclododecanes (HBCDs: α-HBCD + β-HBCD + γ-HBCD), and polybrominated diphenyl ethers (PBDEs). Several BFRs are highly lipophilic persistent organic pollutants (POPs) which have been identified in the aquatic and terrestrial environment including wildlife and humans[1-3]. In exposed organisms including humans toxic effects, bioaccumulation, metabolism, and pharmacokinetics (especially half-life $t_{½}$) are important criterions in the hazard assessment.

The aim of the present study was to estimate the terminal elimination half-lives ($t_{½H}$) of the main BFRs from the whole body (also named body-burden half-life) and/or from the adipose tissue (fat) of adult humans. The $t_{½H}$ data for the following BFRs were evaluated: TBBPA, HBCD, 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), 2,2',4,4',5-pentaBDE (BDE-99), 2,2',4,4',6-pentaBDE (BDE-100), 2,2',4,4',5,5'-hexaBDE (BDE-153), and 2,2',4,4',5,6-hexaBDE (BDE-154).

Material and Methods

The terminal elimination half-lives ($t_{½H}$) of the main BFRs in adult humans were estimated by two independent different methods.

Method I: Estimation of the $t_{½H}$ from body burden and daily intake

The whole body (total body burden) half-lives in humans ($t_{½H}$ in days) of BFRs were estimated from the daily intake (DI in ng × day $^{-1}$) and the total body burden under steady state conditions in

non-occupationally exposed adult humans according to equation (1) for a linear one compartment open pharmacokinetic model:

$$t_{½H} = \frac{\ln 2 \times m_{ss}}{DI \times f} = \frac{0.693 \times c_{ss} \times m_f}{DI \times f} \quad (1)$$

where f is the fraction of dose absorbed from food[17-21], m_{ss} is the total amount (in ng) of the chemical in the whole human body at steady-state, c_{ss} is the concentration ($ng \times kg^{-1}$ lipid) in adult humans, and m_f is the fat mass (13.5 kg for an average adult man and 18.7 kg for an average adult woman). The concentrations in non-occupationally exposed adult Swedish humans were taken from the literature[6]. The daily intake of the five PBDE congeners BDE 47, 99, 100, 153, 154, and of HBCD for adult humans are based on a Swedish market basket study calculated by Darnerud[4] and Lind et al[5].

Method II: Estimation of the $t_{½H}$ in human fat from the $t_{½R}$ in fat of rat
A literature search was conducted to obtain terminal elimination half-lives in rats ($t_{½R}$) for TBBPA, HBCD, TeBDE, PeBDE, and HxBDE.

Method IIa:
In cases were the $t_{½R}$ values are smaller than 10 days the $t_{½}$ in adipose tissue of adult humans are estimated from the rat $t_{½}$ data by multiplying this value by a factor of eight[6].

Method IIb:
If the $t_{½R}$ values of BFRs in fat of rats are greater than 10 days, the terminal $t_{½H}$ in fat and/or blood of adult humans (in days) are estimated from the linear regression equation (2) established for 50 xenobiotics[6]:

$$\log t_{½H} = 1.34 \log t_{½R} + 1.25 \quad (2)$$

where $t_{½R}$ is the terminal half life (in days) in fat of rats ($r^2 = 0.969$; level of significance $P<0.001$).

Results and Discussion

A wide range of tissue concentrations is observed among individuals for PBDEs, HBCD, and other persistent organic pollutants (Table 1). The reason for this variability relate to differences in exposure, total body fat content of humans and host differences that affect bioaccumulation, uptake and elimination[6]. Interestingly, half-life estimates among PBDE-exposed workers were highly variable[9]. Inter-individual differences in rate of removal of PBDEs (e.g., variability in metabolism or diets that break the cycle of enterohepatic circulation[21]) may be major factors explaining the wide variability of PBDE, TBBPA and HBCD levels.
The terminal elimination $t_{½H}$ values estimated by the two different methods I and II are compiled with other relevant data in Tables 1 and 2. It is obvious that the $t_{½H}$ values of the single BFRs obtained by the two methods are in good or satisfactory agreement (see Table 1 and 2). The estimated terminal $t_{½H}$ of TBBPA in blood serum of humans (3.5 days) is in excellent agreement with the experimental $t_{½H}$ value (2.2 days; 95% CI 1.4-2.9 days) in blood serum of workers at an

electronics dismantling plant[7]. However, it is important to note that the $t_{½}$ in plasma and adipose tissue is much longer if ^{14}C-labelled TBBPA is used and all the metabolites are included[10] (see Table 2). For HBCD the terminal total-body elimination half-life ($t_{½H}$) and the terminal half-life from the adipose tissue of adult humans of 64 days (range 22-210 days) is reported here for the first time. The terminal whole-body $t_{½H}$ values of tetra- (BDE-47), penta-(BDE-99), and hexabromodiphenyl ether (BDE-153) estimated by method I are 1.8 years (range: 1.4 - 2.4 y), 2.9 years (range: 1.8 – 4.0 y) and 6.5 years (range: 3.6 - 12,4 y). The $t_{½H}$ values of the same PBDE congeners estimated by method IIb are 3.0 years (range: 1.9 – 4.2 y), 5.4 years (range: 3.5 - 7.2 y) and 11.7 years (range: 7.8 - 15.7 y). These results are in agreement with the prediction of McDonald[8]. It is obvious that the $t_{½H}$ values of these PBDEs are increasing with the number of bromine atoms per molecule. These results are in agreement with other $t_{½}$ data of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polybrominated diphenyl ethers (PBDEs) in experimental animals where increases in halogenation of a molecule generally extend elimination half-lives[6,11,13]. However, it is not possible to compare our whole-body elimination $t_{½H}$ values of lower BDEs with the results of Jakobsson et al.[9], who measured the decrease of higher BDEs in blood serum of Swedish workers during a relatively short time (4-5 week vacation period).

In this context it is important to note, that in 1973 over nine million people were exposed to the BFR Fire Master BP-6™ containing polybrominated biphenyls (PBBs), mainly 2,2',4,4',5,5'-hexabromobiphenyl (HxBB) from food. Between 1974 and 1976 blood of humans were measured for the decrease of PBBs. The half-life ($t_{½H}$) of PBBs in blood of humans during the two years had been estimated in the order of 10 to 11 months[15]. However, the serum $t_{½H}$ of the major PBB congener, 2,2',4,4',5,5'-hexabromobiphenyl (HxBB), was determined by Lambert et al.[16] comparing the current serum HxBB values to the subject's previous serum values obtained 5 to 8 years earlier. The median HxBB $t_{½H}$ in serum was 12 years (range: 4 – 97 y).

Table 1: Terminal total-body elimination half-lives ($t_{½H}$) of hexabromocyclododecane (HBCD) and lower brominated diphenyl ethers (PBDEs) in non-occupationally exposed adult humans estimated from daily intake (DI) and human total body burden of these brominated flame retardants (method I).

Brominated Flame Retardants (BFRs)	Concentration in humans (range)		Daily intake[c] [ng/day]	Fraction of absorption (f)	Total body half-life ($t_{½H}$)[a]	
	Tissue[b]	c_{ss} [ng/kg fat]			[days]	[years]
1,2,5,6,9,10-Hexabromo-cyclododecane (HBCD)	BM	700[d] (250-2400)[d]	142	1.0	64 (23-219)	0.17 (0.06-0.6)
2,2',4,4'-Tetrabromo-diphenyl ether (BDE-47)	AT, BS, BM	1920 (1500-2500)	26.3	0.96	664 (556-926)	1.8 (1.5-2.5)
2,2'4,4',5-Pentabromo-diphenyl ether (BDE-99)	AT, BS, BM	872 (430-1340)	9.09	0.89	1040 (663-1442)	2.9 (1.8-3.95)
2,2',4,4',6-Pentabromo-diphenyl ether (BDE-100)	AT, BM	330 (270-380)	5.41	0.93	573 (469-660)	1.6 (1.3-1.8)
2,2',4,4',5,6-Hexabromo-diphenyl ether (BDE-154)	AT, BP	533 (380-708)	4.61	0.86	1214 (837-1560)	3.3 (2.3-4.3)
2,2',4,4',5,5'-Hexabromo-diphenyl ether (BDE-153)	AT, BS	1193 (570-1990)	4.25	0.90	2380 (1300-4530)	6.5 (3.6-12.4)

[a]The total body half-life ($t_{½H}$) was estimated by equation (1).
[b]Tissue: BM breast milk, AT adipose tissue, BS blood serum, BP blood plasma.
[c]The daily intake of BFRs by adult humans in Sweden is based on a market basket study of Darnerud [4,5].
[d]Barregard et al. (2003)[12]

Conclusions

The presented data suggest that there are differences in retention within the PBDE group and that the terminal human whole-body half-lives ($t_{½H}$) of BDE-47, 99, 100, 153 and 154 are much longer than that for HBCD. Moreover, the presented terminal $t_{½H}$ data, considerably longer than indicated by Jakobsson et. al.[9], indicate that the long retention times of these PBDEs are of concern in the risk assessment of these compounds and that further human exposure should be limited.

Table 2: Terminal elimination half-lives ($t_{½H}$) of brominated flame retardants (BFRs) in blood (BL), plasma (PL) or adipose tissue (AT) of adult humans estimated from measured rat $t_{½R}$ data (method IIa or IIb).

Brominated Flame Retardants (BFRs)	Terminal elimination half-lives in					
	Rats ($t_{½R}$)			Humans ($t_{½H}$)		
	Tissue	Gender[a]	[days]	Method[b]	[days]	[years]
3,3',5,5'-Tetrabromo-bisphenol A (TBBPA)	BL	m	0.43	IIa	3.5	0.01
	BL	m	0.83[c]	IIa	6.6[c]	0.02[c]
	PL	f	9.58[c]	IIa	76.7[c]	0.21[c]
	AT	f	2.63[c]	IIa	21.0[c]	0.058[c]
	AT	m	2.95[c]	IIa	23.6[c]	0.065[c]
1,2,5,6,9,10-Hexabromo-cyclododecane (HBCD: Σ α-, β-, γ-isomers)	AT	m	8.0	IIa	64.0	0.18
Diphenylether (DPE)	AT	m	0.52[c]	IIa	4.2[c]	0.01[c]
	BL	m	0.82[c]	IIa	6.5[c]	0.02[c]
2,2',4,4'-Tetrabromo-diphenyl ether (BDE-47)	AT	m	15.1[g]	IIb	676	1.9
	AT	f	27.6[g]	IIb	1516	4.2
	AT	m + f	21.4[d]	$\bar{x}$ [d]	1096[d]	3.0[d]
	BL	m	31.3[c]	IIb	1795[c]	4.9[c]
2,2',4,4',6-Pentabromo-diphenyl ether (BDE-100)	AT	m	18.5[g]	IIb	887	2.4
	AT	f	23.8[g]	IIb	1243	3.4
	AT	m + f	21.2[d]	$\bar{x}$ [d]	1065[d]	2.9[d]
2,2'4,4',5-Pentabromo-diphenyl ether (BDE-99)	AT	M	24.3[g]	IIb	1279	3.5
	AT	F	41.6[g]	IIb	2628	7.2
	AT	m + f	33.0[d]	$\bar{x}$ [d]	1953[d]	5.4[d]
2,2',4,4',5,6-Hexabromo-diphenyl ether (BDE-154)[e]	AT	m	31.1[g]	IIb	1780	4.9
	AT	f	39.6[g]	IIb	2460	6.7
	AT	m + f	35.4[d]	$\bar{x}$ [d]	2113[d]	5.8[d]
2,2',4,4',5,5'-Hexabromo-diphenyl ether (BDE-153)[f]	AT	m	44.2[g]	IIb	2850	7.8
	AT	f	74.3[g]	IIb	5716	15.7
	AT	m + f	59.3[d]	$\bar{x}$ [d]	4280[d]	11.7[d]

[a]Gender: m male, f female.
[b]Method IIa or IIb see text.
[c]The half-lives for the parent chemical plus the metabolites.
[d]Mean $t_{½}$ values.
[e]The BDE-154 included a PeBDE [probably 2,2',3,4,4'-Pentabromodiphenyl ether (BDE-85)][14], which can be metabolized and eliminated much faster than BDE-154.
[f]The BDE-153 included a HxBDE isomer [probably 2,2',3,4,4',5-hexabromodiphenyl ether (BDE-138)][14], which can be metabolized and eliminated much faster than BDE-153.
[g]These $t_{½R}$ data were measured by Beate Hufnagel[13] during a 70 days elimination phase and are not corrected for the change in body weight of the rats.

Disclaimer:

This short paper has been reviewed in accordance with the California Environmental Protection Agency policy and approved for publication. This paper does not represent California EPA policy.

References

1. Birnbaum L. S., Staskal D. F. (2004) Environ. Health Perspect. 112, 9-17
2. deWit C. A. (2002) Chemosphere 46, 583-624
3. Darnerud P. O. (2003) Environment Intern. 29, 841-853
4. Darnerud P. O. (2004) publication in preparation
5. Lind Y., Aune M., Atuma S., Becker W., Darnerud P. O. (2003) Organohalogen Compounds 58, 181-184
6. Geyer H. J., Schramm K.-W., Feicht E.A., Poiger H., Henkelmann B., Kettrup A. (2002) Chemosphere 48, 631-644 and publication in preparation
7. Hagmar L., Sjödin A., Höglund P., Thuresson K. , Bergman A. (2000) Organohalogen Compounds 47, 198-201
8. McDonald T. (2002) Chemosphere 46, 745-755
9. Jakobsson K., Thuresson K., Höglund P., Sjödin A., Hagmar L., Bergman A (2003) Organohalogen Compounds 61, 17-20
10. Szymansky J. A., Sapota A., Frydrych B. (2001) Chemosphere 45, 693-700 and personal communication
11. Darnerud P. O., Erikson G. S., Johannesson T., Larsen P. O., Viluksela M. (2001) Environ. Health Perspect. 109 (Suppl. 1), 49-68
12. Barregard L., Aune M., Claesson A., Darnerud P. O. (2003) Annual Conference of the International Society of Exposure Analysis. Stresa, Italy Sept. 21-25, 2003. Abstract P1.1-15. Abstract Book
13. Hufnagel B. (1990) Analytical investigations on the retention behavior of dibromobenzyltoluene (DBBT), polychlorobenzyltoluenes (PCBTs), and polybrominated diphenyl ethers (PBDEs) in animals and bacteria suspensions. Doctoral thesis. University of Hamburg, Germany (in German)
14. Sjödin A., Jakobsson E., Kierkegard A., Marsh G., Sellström U. (1998) J. Chromatogr. A 822, 83-89
15. Isbister J. L. (1977) Clin. Medicine 84, 22-24
16. Lambert G. H., Schoeller D. A., Humphrey H. E. B., Kotake A. N., Lietz H., Campbell M., Budd M. (1990) Environ. Health Perspect. 89, 175-181
17. KEMI (2003) Swedish National Chemicals Inspectorate. Risk Assessment – Hexabromocyclododecane. Draft 29 August 2003, Solna, Sweden
18. Moser G. A. (1998) Absorption and excretion of persistent lipohilic environmental pollutants in the human gastro-intestinal tract. Doctoral thesis, University of Bayreuth, Germany (in German)
19. Örn U., Klasson-Wehler E. (1998) Xenobiotica 28, 199-211
20. Hakk H., Huwe J., Lorentzen M. (2001) Organohalogen Compounds 52, 5-8
21. Meijer L., Hafkamp A. M., Bosman W. E., Malmberg K., Bergman A., Sauer P. J. J., Verkade H. J. (2003) Organohalogen Compounds 64, 289-292