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Bounding uncertainties in intrinsic human elimination half-lives and intake of polybrominated diphenyl ethers in the North American population

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ABSTRACT

We examine the balance between intake, intrinsic elimination half-lives and human body burdens measured in biomonitoring for polybrominated diphenyl ethers (PBDEs) in the North American population using the population-level pharmacokinetic model developed by Ritter et al. (2011). Empirical data are collected from two studies that made total intake estimates for the North American population for the years 2004 and 2005, and eight biomonitoring studies for the years 1992 to 2009. We assume intake of PBDEs increased exponentially to a peak in 2004, and has since exponentially declined. The model is fitted to the empirical PBDE intake and biomonitoring data on PBDE body burden using a least-square optimization method by adjusting the intake in 2004 and 2038, and the intrinsic elimination rate constants, which can be expressed as equivalent half-lives. We fit the model in two types of scenarios using different combinations of PBDE intake estimates and biomonitoring data. Our modeling results indicate that there is an inconsistency between the PBDE intake estimates and the biomonitoring data, and that the inconsistency is likely due to underestimation of population-level intake. More efforts are needed to better characterize intake rates and identify potentially-unrecognized exposure pathways. Additional age-stratified biomonitoring data, and time trends of PBDE intakes would better constrain the model and provide an improved estimation of the intrinsic elimination half-lives.

1. Introduction

Persistent organic pollutants (POPs) are present in the bodies of every person on earth (Hites, 2004; Lignell et al., 2009) in amounts that are determined by the balance between the rates of intake and elimination. Understanding and quantifying these competing rates in the general population is an important scientific challenge.

The rate of intake of POPs at the population level is usually estimated from measured chemical concentrations in exposure media (i.e. food, water, air, dust) multiplied by contact rates with relevant pathways (usually inhalation, ingestion and dermal uptake) (Trudel et al., 2011). Intake estimates made in this way require extensive sampling and analysis, but they provide only a 'snapshot' of intakes that are likely to be changing in time.

Measuring the elimination kinetics of POPs in the general population presents even greater conceptual and practical problems. It is not feasible to isolate members of the general population from ongoing exposure and determine elimination kinetics directly from the time-course of declining concentrations in the body because time-scales for elimination are long, typically several years, and exposure occurs via ubiquitous contamination of air, water and food. The closest approximation to such an experiment is to estimate elimination half-lives of POPs from sequential measurements of blood in highly-exposed individuals who have been removed from the source of acute exposure. However, in such studies the estimated half-lives have sometimes been shown to be shorter than in the general population, which could be due to physiological responses to high intakes (Sorg et al., 2009), and alterations in the half-lives with time as background exposure becomes non-negligible (Matsumoto et al., 2009; Seals et al., 2011). Recognizing these problems, Shirai and Kissel (1996) introduced the term "apparent elimination half-life" to refer to empirically-derived elimination half-lives that may be confounded by ongoing exposure. Later, Ritter et al. (2011) extended the definition to also include the possible effects of changes in body weight and lipid-mass of the measured individuals on empirically-derived apparent half-lives.

A further complication is that apparent elimination half-lives are not directly relevant for building an understanding of the balance between rates of intake and elimination of POPs at the general population level because they describe the observed decline in concentration under specific conditions of ongoing expo sure and changes in body size and composition. The more relevant parameter is the "true" (Shirai and Kissel, 1996) or "intrinsic" (Ritter et al., 2011) elimination half-life that is not confounded by ongoing exposure and changes in body condition.

Recently, Ritter et al. (2009, 2011) developed a population-level pharmacokinetic (PK) model (hereafter called the "Ritter model") that quantitatively describes the three defining characteristics of human

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exposure and biomonitoring assessments: 1) body burden measured in biomonitoring, 2) the level and temporal trend of population-level intake rate and 3) the intrinsic half-life for elimination of a chemical from the human body. The Ritter model was previously evaluated and demonstrated by calculating intrinsic elimination half-lives for polychlorinated biphenyls from empirical intake estimates and biomonitoring datasets for the UK population (Ritter et al., 2011). Quinn and Wania (2012) used a similar model to show that if intake and intrinsic elimination half-lives are known then biomonitoring data can be reconstructed. However, in principle such models can be used to estimate any one of the defining characteristics (i.e., intake, body burden, or intrinsic elimination half-life) if the other two are specified.

Although polybrominated diphenyl ethers (PBDEs) are among the most-studied flame retardants over the past decade in human exposure assessments, their pharmacokinetics in the human body are not well characterized. Estimates of elimination half-lives for PBDEs in humans were extrapolated from a rat study (Geyer et al., 2004), and apparent elimination half-lives were reported from a study that followed PBDE levels in occupationally-exposed individuals (Thuresson et al., 2006). Others have combined biomonitoring and intake studies to estimate elimination half-lives of PBDEs using steady-state PK models (Trudel et al., 2011). The half-life estimates reported for individual PBDE congeners in these studies vary 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 literature half-lives are not consistent with intake estimates (Fromme et al., 2009; Lorber, 2008; McDonald, 2005; Toms et al., 2008), which may be a result of uncertainty in the elimination half-lives, intake estimates, or both.

Here, we fit the Ritter model to intake estimates and biomonitoring data for the North American population. We present two model scenarios with the goals to: i) assess the consistency of intake, elimination half-lives and biomonitoring data, and ii) constrain uncertainties on the intake estimates and the intrinsic human elimination half-lives of PBDEs.

2. Materials and methods

2.1. Biomonitoring data

Biomonitoring data for PBDE body burdens are collected from eight studies conducted between 1992 and 2009 in the general population of North America (Table 1). Four of the eight studies reported PBDE concentrations in breast milk; the other four reported serum PBDE concentrations. To combine the datasets we assume that lipid-normalized PBDE concentrations in serum and milk are equal, which would be the case if the two lipid compartments are in equilibrium (Schecter et al., 2010; Wittsiepe et al., 2007). The most comprehensive biomonitoring data is the National Health and Nutrition Examination Survey (NHANES), which reports PBDEs in serum of more than 2000 individuals in the United States with age-stratified cohorts (Sjödin et al., 2008). In studies where no information about the age of the sampled individuals is available, we assume the average age of a mother who provided the milk sample is 25 (Mathews and Hamilton, 2002). The median age of the US population of 35 was used for individuals who provided serum samples (The World Factbook, 2009).

2.2. Intake data

Congener-specific daily intake for the North American population has previously been estimated in two total intake studies (Table 2). Estimates from Trudel et al. (2011) were derived from PBDE concentrations measured from 2001 to 2010, while those from Lorber (2008) were from studies conducted from 2002 to 2006. For fitting the Ritter pharmacokinetic model, we assume that the Trudel and Lorber studies are representative of intakes in the years 2005 and 2004, respectively. Intake pathways considered in the studies include ingestion of food and dust/soil, inhalation of air, and dermal contact with dust/soil and surface films. The congener profile of total PBDE intake estimated by Trudel et al. (2011) is assumed to be the same as Lorber (2008), i.e. BDE-47 (26%), BDE-99 (28%), BDE-100 (11%), BDE-153 (3%).

Table 1
Details of biomonitoring datasets of human serum and milk sampled from 1992 to 2009.

Sampling year	Sample type	Age range	Sample size	Location	Reference
1992[a]	Milk	25[i]	1	Canada	Ryan and Patry, 2000; Ryan et al., 2002
2001[b]	Milk	20–41	47	US	Schecter et al., 2005
2002[c]	Milk	25[i]	20	Canada	Ryan et al., 2002
2004[d]	Milk	25[i]	12	US	Schecter et al., 2005
2004[e]	Serum	12–79	2197	US	Sjödin et al., 2008
2007[f]	Serum	25[i]	29	US	Schecter et al., 2010
2008[g]	Serum	35[i]	24	US	Johnson et al., 2010
2009[h]	Serum	35[i]	31	US	Watkins et al., 2011

[a] Pool of 271 milk samples from Canada. The median of total PBDEs (47, 99, 153, 100, 28, 154, 183) was reported and specific PBDE congener concentration was calculated.
[b] Milk samples from Texas, US. Concentrations of specific PBDE congener in individual samples were reported. The data were aggregated into two age groups and the geometric mean for each group was calculated.
[c] Milk samples from Vancouver, Canada. The mean of total PBDEs (47, 99, 153, 100, 28, 154, 183) was reported and specific BDE congener concentration was calculated.
[d] Milk samples from Texas, US. Concentrations of specific PBDE congener in individual samples were reported.
[e] Serum samples from US. Concentrations of specific PBDE congener in individual samples were reported. The data were aggregated into 7 age groups and the geometric mean for each group was calculated.
[f] Serum samples of mothers from Texas, US. Concentrations of specific PBDE congener in individual samples were reported. The geometric mean was calculated.
[g] Serum samples from Massachusetts, US. Samples were analyzed individually and the geometric mean of specific PBDE congener was reported.
[h] Serum samples from Massachusetts, US. Samples were analyzed individually and the geometric mean of specific PBDE congener was reported.
[i] No information on the age of individual who supplied the samples was available. The assumed age for mothers who provided milk sample is 25 and for the general population who provided serum sample is 35.

2.3. The Ritter et al. (2011) population pharmacokinetic model

The Ritter model treats representative humans in a population as single, well-mixed compartments for chemicals and assumes that chemicals are distributed at equilibrium within body lipids. In its most

Table 2
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)				
Lorber, 2008	1.98	2.19	0.83	0.23
Trudel et al., 2011 (Median)	0.44	0.48	0.19	0.051
This study—Scenario 2a	54	2.39	2.98	2.44
This study—Scenario 2b: Minimum intake, assuming $t_{1/2} = 15$ years	3.88	1.59	1.17	1.37
This study—Scenario 2c: Using $t_{1/2}$ from Geyer et al. (2004)[a]	8.87	1.97	1.61	1.46
Human elimination half-lives (years)				
Geyer et al., 2004; [a]	3	5.4	2.9	11.7
Geyer et al., 2004; [b]	1.8	2.9	1.6	6.5
Trudel et al., 2011 (Median); [b]	1.4	0.77	1.8	7.4
This study—Scenario 2a	0.37	8.2	2.0	3.5

Note: In Scenarios 2a–c, model is fitted to biomonitoring data only. For 2a) intake and $t_{1/2}$ are optimized, 2b) intake are optimized and $t_{1/2}$ constrained to 15 years, and 2c) intake are optimized and $t_{1/2}$ is constrained to those derived by Geyer et al. (2004) from a rat study.
[a] Derived from experimental studies on rats.
[b] Based on steady-state pharmacokinetic model by using biomonitoring data and population intake estimates.