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Calculation of chemical elimination half-life from blood with an ongoing exposure source: The example of perfluorooctanoic acid (PFOA)

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ABSTRACT

Determination of the chemical clearance rate from human blood is a critical component of toxicokinetic exposure assessment. Analysis of temporal biomonitoring data without consideration of ongoing exposure results in calculation of apparent elimination half-life values that are longer than the intrinsic value. The intrinsic elimination half-life is solely a function of the rate of elimination while the apparent elimination half-life reflects the processes of both elimination and ongoing exposure. Confusion between intrinsic and apparent half-life values can lead to misinterpretation of biomonitoring data and can result in exaggerated predictions in subsequent modeling efforts. This work provides a review of the first-order equations that have been developed to calculate intrinsic and apparent half-life values and the potential bias that can result from confusing these two values. Published human biomonitoring data for perfluorooctanoic acid (PFOA) are analyzed using these equations to provide examples of low, medium and high bias in determination of the intrinsic elimination half-life from plasma or serum, the components of blood typically analyzed for PFOA. An approach is also provided to estimate the extent of exposure reduction that is indicated by declining longitudinal or cross-sectional biomonitoring data. Based on the evaluation methodology presented in this work, the intrinsic elimination half-life of PFOA in humans is 2.4 years, representing the average of independent estimates of 2.5 years (95% CI, 2.4–2.7) and 2.3 years (95% CI, 2.1–2.4). The declining concentration of PFOA in blood of the general USA adult population represents an estimated exposure reduction of 20–30% over the period 1999–2008.

1. Introduction

One of the critical parameters in toxicokinetic assessment of chemical exposure is determination of the rate of clearance from the body *via* a combination of metabolism, conjugation and physical elimination. In biomonitoring studies, internal chemical concentrations are routinely determined as a longitudinal or cross-sectional series of samples from a readily accessible tissue such as blood, plasma or serum. After the cessation of exposure, the rate of elimination can then be determined from mathematical analysis of the time course of the samples. However, in many situations there is some level of ongoing exposure which results in an 'apparent' rather than the 'intrinsic' elimination half-life.

Researchers have previously pointed out that apparent half-life values are functions of both the ongoing rate of uptake as well as the rate of elimination, resulting in biased estimation of the intrinsic elimination half-life (Shirai and Kissel, 1996). However, failure to explicitly account for ongoing exposure is common in the published literature. The rate of intrinsic elimination can be determined if the influence of ongoing exposure and changes in physiology (such as body weight) are accounted for. Population-based pharmacokinetic models have been developed (Ritter et al., 2011) to calculate the intrinsic elimination half-lives of polychlorinated biphenyls in the U.K. population and perfluorooctane sulfonic acid in the U.S. population (Wong et al., 2014). The following discourse provides a review of simple first-order equations for analysis of apparent and intrinsic half-life values, similar to the relationships

Abbreviations: PFOA, perfluorooctanoic acid; Intrinsic elimination half-life, the first-order elimination half-life obtained from the depuration of a chemical from biota when the effects of ongoing exposure are not present or are negligible; Apparent elimination half-life, the first-order elimination half-life obtained from the depuration of a chemical from biota when the effects of ongoing exposure are neglected; Bias, the difference between the apparent elimination half-life and the intrinsic half-life, typically expressed as a normalized percent of the intrinsic value.

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originally developed by Shirai and Kissel. These equations are then used to assess the potential bias in using apparent half-life values to represent intrinsic half-life and to estimate the extent of exposure reduction from temporal biomonitoring data. Similar equations are applicable to environmental systems such as lakes and soil which have simultaneous chemical inputs (i.e., inflow or deposition) and outputs (i.e., outflow, degradation or leaching) (Schnoor, 1996).

The application of these equations is illustrated through examination of three sets of published biomonitoring results for perfluorooctanoic acid (PFOA, CAS 000335-67-1) in human plasma and serum samples. The developed kinetic equations are equally valid for analysis of biomonitoring data for concentrations in blood, plasma or serum. Human biomonitoring for PFOA currently represents one of the most robust datasets available and provides an excellent example of the issue of potential bias in the calculation of elimination rates.

2. Methods: Derivation of equations

2.1. Calculation of blood concentration in response to a constant exposure source

The following equations are similar to mathematical relationships that were originally developed to clarify differences between the intrinsic ('true') and apparent elimination half-lives of PCBs from humans (Shirai and Kissel, 1996). Continuous exposure to a chemical contaminant and subsequent uptake and distribution of that chemical into body tissues commonly leads to an increasing concentration C of the chemical in human blood (or plasma or serum). When chemical exposure is constant or nearly constant and elimination is first order, the rate of change of concentration with time (ng L^{-1} d^{-1}) is given by:

$$dC/dt = I_0 E_a/(V_d M) - k_e C \quad (1)$$

where I_0 is the rate of chemical exposure (ng d^{-1}), E_a is a dimensionless chemical uptake fraction which accounts for the fraction of the chemical exposure that is absorbed into blood, V_d is the volume of distribution (L kg^{-1}) of the chemical and M is body mass (kg). k_e is the intrinsic elimination rate constant (d^{-1}) which describes the underlying rate of chemical loss due to the combination of physical elimination and metabolism. This equation accounts for the difference between constant chemical exposure and first order chemical loss from blood.

Approximate values of V_d include 0.08 L kg^{-1} for a chemical that is distributed solely to human blood and 0.20 L kg^{-1} for distribution to extracellular fluid (i.e. blood, lymph and other fluids) (Wagner, 1975; Brown et al., 1997). Integration of Eq. (1) yields:

$$C(t) = C_0 e^{-k_e t} + C_{ss}(1 - e^{-k_e t}) \quad (2)$$

where $C_{ss} = I_0 E_a/(k_e V_d M)$ and C_0 is the chemical concentration in blood at any given initial time taken to be $t = 0$ for convenience.

2.2. Calculation of steady-state blood concentration for initial chemical exposure

If no chemical is initially present in blood, $C_0 = 0$ and the blood concentration increases with time, asymptotically approaching a steady-state value C_{ss} after an extended period of constant exposure (Fig. 1a). Eventually, the rate of chemical elimination approaches the rate of chemical uptake and the blood concentration stabilizes at the steady-state concentration C_{ss}:

$$\lim_{t\to\infty} C(t) = C_{ss} = I_0 E_a/(k_e V_d M) \quad (3)$$

Eq. (3) is a simple, one-compartment toxicokinetic (TK) model that is routinely used to calculate the chemical concentration in blood in response to a constant or chronic chemical exposure rate I_0. This model can be applied if the fractional chemical uptake (E_a), the rate of elimination and metabolism (k_e), the volume of distribution (V_d) and body mass (M) are known or can be reliably estimated. One-compartment TK models have been applied to estimate human blood concentrations of a wide variety of environmental contaminants that result in chronic, constant or near-constant exposure including pesticides (Timchalk, 2010), brominated flame retardants (Quinn and Wania, 2012; Bjerregaard et al., 2013), perfluoroalkyl substances (Egeghy and Lorber, 2011), dioxin-like chemicals (Olsen, 2012) and polycyclic aromatic hydrocarbons (Li et al., 2012).

2.3. Calculation of blood concentration when constant exposure ceases

When constant chemical exposure has continued for a considerable amount of time, the chemical concentration in blood $C(t)$ approaches its steady state concentration, C_{ss}. Now consider the transient response in blood concentration if chemical exposure suddenly stops or is very significantly reduced. This situation may occur for a number of reasons. A factory worker with high occupational exposure may retire or move to a new assignment with little or no exposure. A person may move from a city with significant local exposure to a different city with no further exposure or they may remain in the same location but exposure is suddenly eliminated by a treatment method (*e.g.* a carbon filter is placed on drinking water).

If chemical uptake abruptly ceases, the subsequent elimination of the contaminant from blood is given by:

$$dC/dt = -k_e C \quad (4)$$

The solution of this first-order differential equation is:

$$C(t) = C_0 e^{-k_e t} \quad (5)$$

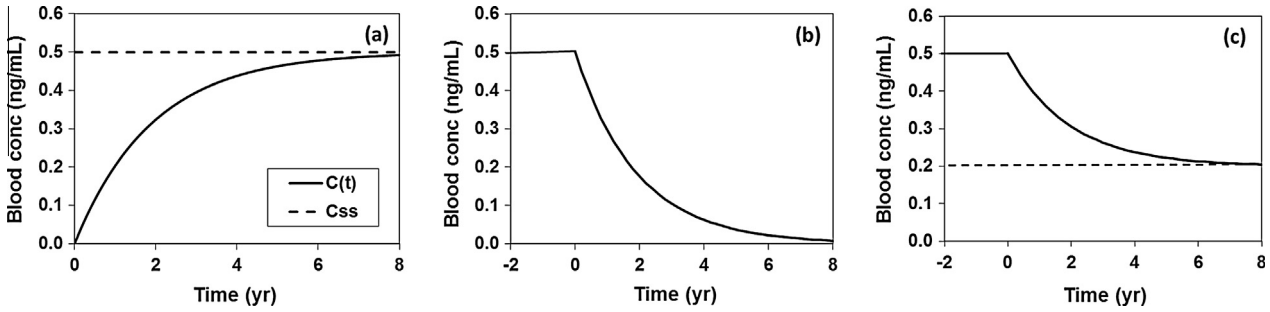

Fig. 1. Example profiles of blood concentrations in response to (a) a constant exposure source, (b) cessation of steady-state exposure and (c) fractional reduction of steady-state exposure. Dashed line is steady-state concentration and solid line is transient concentration.

where C_0 is defined as the chemical concentration in blood at the time when exposure ends, again taken to be $t = 0$ for convenience. This behavior is illustrated in Fig. 1b where C is constant during the period of exposure but then follows a first order decline towards zero when exposure ceases.

2.4. Calculation of blood concentration when exposure is reduced but not fully eliminated

Suppose as before that constant exposure has produced a constant blood concentration C_{ss0}. At time t_0 exposure is markedly reduced but not completely eliminated. When chemical exposure is reduced from an initial constant value (I_0) to a lower but non-zero constant value (I_1), the following expression can easily be derived from Eq. (2):

$$C(t) = C_{ss1} + (C_{ss0} - C_{ss1})e^{-k_e t} \quad (6)$$

where $C(t)$ is the chemical concentration in blood at any time t subsequent to t_0 and C_{ss1} is the new asymptotic steady-state blood concentration associated with the reduced constant exposure input I_1. C_{ss0} and C_{ss1} are easily obtained from Eq. (3) if I_0 and I_1 are known. If the exposures are not known, C_{ss0} can be taken to be the initial blood concentration $C(t_0)$ of the more highly exposed sub-population being studied and C_{ss1} as the background blood concentration measured in the general public. Uncertainty in the values of C_{ss0} and/or C_{ss1} results in uncertainty in the calculated concentration values, $C(t)$, especially when the magnitude of change is small.

Eq. (6) shows that reducing the chemical dose rate from I_0 to I_1 leads to an exponential decrease in blood concentration from an initial steady-state value C_{ss0} to a new, lower steady-state value C_{ss1}. This behavior is illustrated in Fig. 1c. Solving Eq. (6) for k_e yields the following expression:

$$k_e = \ln\left(\frac{C_{ss0} - C_{ss1}}{C(t) - C_{ss1}}\right)/t \quad (7)$$

k_e is the intrinsic elimination rate constant for blood and reflects the actual rate at which chemical is removed from blood *via* the combination of metabolism and physical elimination. The corresponding intrinsic elimination half-life is $t^e_{1/2} = \ln(2)/k_e$.

In many studies, the rate of elimination is evaluated without considering the potential impact of any ongoing source of exposure. Therefore, a conventional first-order equation analogous to Eq. (5) is typically applied:

$$C(t) = C_{ss0}e^{-k_a t} \quad (8)$$

where k_a is the apparent elimination rate constant, the best estimate of the chemical elimination rate constant when ongoing exposure is neglected. Solving Eq. (8) for k_a gives

$$k_a = \ln\left(\frac{C_{ss0}}{C(t)}\right)/t \quad (9)$$

and a corresponding apparent elimination half-life $t^a_{1/2} = \ln(2)/k_a$.

Values of k_a are frequently estimated from only two data points: an initial blood concentration (i.e. C_{ss0}) and a concentration at some later time, i.e. $C(t)$. If there is no ongoing source of exposure, $C_{ss1} = 0$ and $k_a = k_e$. However, if exposure is decreased but not eliminated then $k_a < k_e$, that is, the apparent rate of elimination is slower than the intrinsic rate of elimination. As a result, the apparent elimination half-life is always longer than the intrinsic half-life. Proof of this relationship is provided in the Supplementary Data (SD).

2.5. Bias in calculation of intrinsic elimination half-life

When the contribution of an ongoing source of exposure is ignored, the bias in calculating accurate values of the intrinsic blood elimination half-life can range from minor to extreme. The bias can be estimated from the following relationship:

$$\text{Bias}\,(\%) \equiv 100\left(\frac{k_e - k_a}{k_e}\right) = 100\left(1 - \frac{t^e_{1/2}}{t^a_{1/2}}\right) \quad (10)$$

Estimated values of k_a and the percent bias depend on the sampling time t. In contrast, k_e is an intrinsic quantity and can generally be assumed to be invariant with time (see later discussion for possible longer-term variation in k_e). Estimation of k_e using k_a values from the flawed model described by Eq. (9) leads to two difficulties: k_a systematically underestimates k_e, and the degree of underestimation depends on the times at which blood samples are taken.

For highly exposed individuals who are subsequently removed from any further significant exposure (i.e. $C_{ss0} \gg C_{ss1}$), the calculated percent bias in the elimination half-life is low throughout the initial period of depuration. When the initial steady-state concentration C_{ss0} is 100 times greater than the final steady-state concentration C_{ss1}, the percent bias varies in the range of 1.4–2.2% for sampling times which range over 1–2 intrinsic half-lives (i.e. for the first 50–75% of the change to the new steady-state) (Calculation provided in SD). When the initial to final steady-state ratio is small, the percent bias increases rapidly: if C_{ss0} is 5 times larger than C_{ss1}, the bias increases to 29–50% for the same time frame. In each case where there is an ongoing source, the intrinsic elimination half-life is shorter than the apparent elimination half-life.

This analysis shows that the most accurate estimations of blood elimination half-lives for xenobiotic chemicals will be obtained by examining highly exposed individuals who are subsequently exposed to only minor background concentrations, or from more marginally exposed individuals who are completely removed from any further exposure. The bias in these half-life calculations is generally negligible or is within experimental error. In contrast, attempts to determine intrinsic chemical elimination half-lives from evaluations of moderate to minor reductions in the blood concentrations of the general population will be highly biased and will result in excessively long estimates of intrinsic elimination half-lives.

3. Results: Applying the bias equations to human biomonitoring of PFOA

Bias in calculation of intrinsic elimination half-life values is best illustrated with actual examples. Blood monitoring studies can provide datasets useful for estimation of intrinsic elimination half-lives, especially if information on the relative contribution of ongoing exposure sources is also available. The extensive human biomonitoring data for PFOA provide a unique set of results to demonstrate the potential bias in estimation of intrinsic elimination half-lives inherent in different types of temporal biomonitoring studies.

3.1. Example of minimal bias in intrinsic half-life calculation of PFOA

The results summarized in Table 1 are from a study of recently retired workers who were occupationally exposed to PFOA and other fluorinated chemicals (Olsen et al., 2007). The initial serum concentrations of these individuals ranged between 72 and 5100 ng mL^{-1} PFOA and many workers had initial concentrations greater than 100 times the population background concentration of 4.06 ng mL^{-1} estimated from NHANES data for the general population in the USA during the same time frame (CDC, 2012). For workers with initial serum concentrations >500 ng mL^{-1}, the estimated calculation bias between the apparent and intrinsic elimination half-lives is less than 1.2% indicating that correction

Table 1
Example of negligible calculation bias between apparent and intrinsic elimination half-life values for PFOA (data from Olsen et al., 2007).

Population and sample collection period	Serum concentration (ng mL^{-1})			Elapsed time (yr)	$t^{a}_{1/2}$, apparent elimination half-life, (yr)[†]	$t^{e}_{1/2}$, intrinsic elimination half-life (yr)[‡]	Estimated calculation bias (%)[§]
	Initial	Final	Bkgd[*]				
Retired workers with occupational exposure to PFOA, 1998–2004	5100	2435	4.06	4.78	4.48	4.47	0.12
	1833	486	4.06	5.33	2.78	2.77	0.46
	1622	577	4.06	5.33	3.57	3.56	0.44
	1180	145	4.06	4.74	1.57	1.55	1.18
	1077	404	4.06	4.74	3.35	3.33	0.64
	883	266	4.06	5.33	3.08	3.05	0.89
	702	248	4.06	4.18	2.78	2.75	1.02
	549	235	4.06	4.74	3.87	3.83	1.17
	496	284	4.06	5.27	6.56	6.48	1.10
	490	129	4.06	5.27	2.74	2.69	1.74
	474	162	4.06	5.33	3.44	3.39	1.54
	430	108	4.06	5.33	2.67	2.62	2.04
	425	162	4.06	5.33	3.83	3.77	1.61
	390	61	4.06	4.18	1.56	1.51	3.05
	356	244	4.06	5.33	9.78	9.64	1.39
	306	188	4.06	5.33	7.58	7.45	1.71
	254	150	4.06	3.12	4.11	4.02	2.11
	247	104	4.06	5.33	4.27	4.16	2.62
	212	84	4.06	5.33	3.99	3.86	3.16
	183	50	4.06	5.33	2.85	2.72	4.58
	181	65	4.06	5.33	3.61	3.47	3.92
	167	78	4.06	5.33	4.85	4.67	3.65
	142	51	4.06	5.33	3.61	3.43	5.00
	131	45	4.06	5.33	3.46	3.26	5.57
	74	26	4.06	5.33	3.53	3.19	9.78
	72	17	4.06	5.33	2.56	2.23	12.96
Workers with initial serum concentration > 500 ng mL^{-1} -		Geomean:		3.06	3.04}	0.6	
		95% CI:		(2.46–3.81)	(2.44–3.79)		
All workers -		Geomean:		3.56	3.46}	2.8	
		95% CI:		(3.06–4.16)	(2.96–4.05)		

[*] Background PFOA plasma values are geomean averages of NHANES data for 1999–2004: Geomean of adults 60+, 1999–2004 = 4.06 ng mL^{-1}.
[†] Calculated with Eq. (9). Values differ slightly from Olsen et al. values which were determined by linear regression with multiple data points.
[‡] Calculated with Eq. (7).
[§] Calculated with Eq. (10).

of the observed serum concentrations for background exposure has a negligible effect. However, for those individuals with lower initial serum concentrations, the calculation bias ranges up 13%. It should be noted that minimal bias values (i.e. <10–15%) are likely to be similar to the uncertainty in analytical measurements.

The apparent geometric mean elimination half-life for all workers reported by Olsen et al. was 3.5 years (95% CI, 3.0–4.1) (Olsen et al., 2007). However, if the calculations are restricted to only those workers with initial serum concentrations greater than 500 ng mL^{-1}, a less-biased estimate of the intrinsic half-life of PFOA is 3.0 years (95% CI, 2.4–3.8). Due to the highly elevated initial concentration and the extended sampling duration (almost two half-lives), the intrinsic elimination half-life determined from these highly exposed individuals is expected to provide an accurate estimate of the elimination rate of PFOA from this population of male adults.

3.2. Example of moderate bias in intrinsic half-life calculation of PFOA

An example of moderate calculation bias in elimination half-lives can be found in the recent study of residents of Arnsberg, Germany who were environmentally exposed to PFOA through drinking water during the period 2006–2008 (Brede et al., 2010). The geometric mean PFOA apparent elimination half-life for the adult participants in Arnsberg was 3.2 years (95% CI, 2.9–3.5) (Table 2). Adjusting for background exposure from the reported control population provides a geometric mean intrinsic elimination half-life of 2.5 years (95% CI, 2.4–2.7) for adults. In this case the initial plasma PFOA concentrations were 5–8 times higher than the estimated background plasma concentrations in the control population and the sampling interval was less than one half-life. For the Arnsberg study, neglecting to correct for the observed background concentrations resulted in a mean calculation bias of 21% for the adult population.

In a similar study of adult residents in the Mid-Ohio Valley of the USA who were exposed to PFOA in drinking water, the apparent elimination half-life was observed to vary with both time and concentration, leading to an initial conclusion that the clearance of PFOA may be concentration dependent or the result of ongoing background exposure (Seals et al., 2011). When the observed biomonitoring results were analyzed using a statistical model that accounted for ongoing exposure, the mean elimination half-life was estimated to be 2.3 years (95% CI, 2.1–2.4) (Bartell et al., 2010). This half-life result is in excellent agreement with the value determined above for the Arnsberg population. An average intrinsic elimination half-life of 2.4 years from the results from the Arnsberg and Ohio Valley studies provides a reasonable estimate to be used for comparison with other temporal biomonitoring studies of PFOA for the general population.

3.3. Example of high bias in intrinsic half-life calculation of PFOA

An example of high bias in estimated PFOA elimination half-lives is shown in Table 3. These cross-sectional data were

Table 2
Example of moderate calculation bias between apparent and intrinsic elimination half-life values for PFOA (from Brede et al., 2010).

Population and sample collection period	Sub-population *	Plasma concentration (ng mL^{-1})			Elapsed time (yr)	Apparent elimination half-life, (yr)	Intrinsic elimination half-life (yr)	Calculation bias (%)
		Initial	Final	Bkgd†				
Arnsberg residents, 2006–2008	Children (20)	23.4	13.2	5.0	2.00	2.42	1.72	29.2
	Mothers (22)	23.6	13.3	2.9	2.00	2.42	2.01	16.7
	Men (23)	30.3	21.7	6.3	2.00	4.15	3.13	24.6
				All sub-populations:	{Geomean: 95% CI:	2.93 (2.75–3.12)	2.24 (2.10–2.39)	23.5
				Adults only:	{Geomean: 95% CI:	3.19 (2.94–3.45)	2.52 (2.36–2.69)	20.9

* Number of individuals in the population given in parentheses.
† Background PFOA plasma values are the geomean of the control population in Siegen Germany.

Table 3
Example of high calculation bias between apparent and intrinsic elimination half-life values for PFOA (from Kato et al., 2011).

Population and sample collection period	Sub-Population*	Serum concentration (ng mL^{-1})		Elapsed time (yr)	Apparent elimination half-life (yr)	Intrinsic elimination half-life † (yr)	Calculation bias (%)
		Initial	Final				
USA general population, 1999–2008	Males	5.71	4.80	8.0	31.9	2.4	92
	Females	4.80	3.56	8.0	18.6	2.4	87
	nHW‡	5.60	4.38	8.0	22.6	2.4	89
	MA‡	3.89	3.53	8.0	57.1	2.4	96
	nHB‡	4.80	3.86	8.0	25.4	2.4	91
						Mean bias: 95% CI:	91 (87–95)

* All individuals in the study were >12 years old.
† The intrinsic elimination half-life was determined to be 2.4 years, the average of the general population data of Bartell et al. (2010) and Brede et al. (2010).
‡ Key: nHW (non-Hispanic Whites); MA (Mexican–Americans); nHB (non-Hispanic Blacks).

compiled by the U. S. Centers for Disease Control and Prevention (CDC) as a part of the National Health and Nutritional Evaluation Survey (NHANES) (Kato et al., 2011). NHANES data from the years of 1999–2008 showed a general downward trend in PFOA serum concentrations for the U.S. general population. Geometric mean PFOA concentrations in males 12 years of age or older fell from 5.71 ng mL^{-1} in 1999–2000 to 4.47 ng mL^{-1} in 2003–2004 but remained largely unchanged from 2003 to 2008. Serum PFOA concentrations in females 12 years of age or older were lower than those found for males but followed the same general trend. These changes reflect a general reduction in exposure to polyfluoroalkyl chemicals which is most likely due to changes in manufacturing practices and product formulation that began in 2002.

PFOA is a persistent chemical and there is direct, ongoing exposure to legacy PFOA in the environment. In addition, ongoing indirect sources of PFOA have been identified such as formation from precursor chemistry (Prevedouros et al., 2006). The NHANES data indicate that PFOA uptake has been reduced since 1999 but ongoing exposure to legacy and indirect sources remains. As a result, calculation of the apparent elimination half-life of PFOA from the gradual decline observed in the general population provides a misleading estimate of the intrinsic elimination half-life with a mean calculation bias of 91% (95% CI, 87–95) (Table 3). The Mexican–American (MA) sub-population shows a PFOA concentration decline of less than 10% (geomean values of 3.89 ng mL^{-1} declining to 3.53 ng mL^{-1}) which leads to a highly biased (and highly inaccurate) value of the intrinsic elimination half-life for this sub-population. The calculation biases summarized in Table 3 result almost entirely from neglecting ongoing PFOA exposure as concentrations in the general population are observed to slowly decline.

3.4. Using biomonitoring data to estimate chemical exposure reduction

Eq. (6) describes how a partial reduction in chemical exposure leads to a reduction in blood concentration. In the derivation of Eq. (6) it was noted that the initial and final steady state concentrations (C_{ss0} and C_{ss1}) can be readily obtained from the generic expression $C_{ss} = IE_a/(k_e V_d M)$ when the initial and final chemical exposure rates (I_0 and I_1) are known. The inverse proposition also holds: initial and final chemical exposures can be obtained if initial and final steady state blood concentrations are known. In fact, the ratio of the initial and final exposure rates is equal to the ratio of the initial and final steady state concentrations, that is

$$I_1/I_0 = C_{ss1}/C_{ss0} \tag{11}$$

The ratio of C_{ss1} to C_{ss0} can be obtained from Eq. (6) and the resulting percentage exposure reduction (ER) is then given by:

$$\mathrm{ER}(\%) \equiv 100(1 - I_1/I_0) = 100\left(\left(1 - \frac{C(t)}{C_{ss0}}\right)/\left(1 - e^{-k_e t}\right)\right) \tag{12}$$

In Eq. (12), t is the time that has elapsed since exposure was reduced. Eq. (12) shows that, within the limitations of this simple model, exposure reduction can be calculated directly from measurements of $C(t)$ if the intrinsic elimination rate constant, k_e, the initial steady state concentration, C_{ss0}, and the elapsed time since exposure reduction, t, are known. In practice, C_{ss0} and t can be estimated by examination of the time history of blood concentration to find the onset of reduction in $C(t)$: C_{ss0} can be taken as the mean value of $C(t)$ before the blood concentration changed and t can be taken as the elapsed time since the onset of reduction of $C(t)$.

The derivation of Eqs. (11) and (12) is given in the SD. Eq. (12) can be used to estimate the exposure reduction of many additional environmental contaminants such as lead, cotinine and benzene

for which extensive biomonitoring data have been collected and reported in studies such as NHANES.

3.5. Estimating exposure reduction of PFOA in USA general population

As discussed above, the intrinsic PFOA half-life for the general population is 2.4 years resulting in $k_e = \ln(2)/2.4 = 0.289\ yr^{-1}$. The NHANES data summarized for males and females in Table 3 were collected over an eight year period (i.e. $t = 8$). When these values are substituted into Eq. (12), the estimated exposure reduction for the general US male population is 18% and the corresponding final steady-state serum concentration is $4.7\ ng\ mL^{-1}$. For females 12 and older, a similar calculation results in an estimated exposure reduction of 29% and a corresponding final steady state serum concentration of $3.4\ ng\ mL^{-1}$. Apparent sex-based differences in PFOA exposure reduction may reflect differences in exposure scenarios, limitations in the modeling assumptions, uncertainty and bias in the monitoring data as well as actual differences in intrinsic elimination rates for men and women. Based on these inverse calculations, it is reasonable to conclude that PFOA exposure in the general US adult population decreased by 20–30% over the period 1999–2008. The estimated exposure reduction is similar to the change in male and female body burdens of PFOA over this period, as reflected in the decrease in serum concentrations, i.e. 16% and 26% for males and females, respectively. Due to the multi-year intrinsic elimination half-life of PFOA, the observed decline in serum concentration lags the estimated reduction in external exposure over the nine period of biomonitoring.

4. Discussion

As demonstrated in the examples described above, accurate determination of intrinsic chemical elimination half-life values is a function of the magnitude of observed concentration decline as well as the level of ongoing exposure (Eq. (7)). Accurate calculation of intrinsic elimination half-life values requires both an extended period of sampling (i.e. more than 1–2 half-lives) and appropriate correction for ongoing exposure. Alternatively, intrinsic elimination half-life values can be derived from multiple cross-sectional biomonitoring and intake data by using population-level pharmacokinetic modeling as demonstrated for human exposure to polychlorinated biphenyls (Ritter et al., 2011).

The intrinsic elimination half-life is not necessarily the same in all sub-populations. For chemicals such as PFOA which are eliminated almost exclusively *via* urinary excretion, it is important to consider the age and gender of the population being studied. The glomerular filtration rate (GFR) of the kidney typically decreases with age (Sun et al., 2009; Musso and Oreopoulos, 2011). In addition, differences in the elimination half-life of PFOA have been noted between males and females. Enhanced elimination of PFOA in menstruating women is possible as several studies have reported lower PFOA levels in women than men (Harada et al., 2005; Yeung et al., 2006; Kato et al., 2011). Furthermore, mean elimination half-lives of PFOA have been estimated to be slower for young females (2.1 yr) than for males or older females (2.6 yr) (Zhang et al., 2013). These factors may help explain the differences observed between the intrinsic elimination half-lives calculated for PFOA in older, predominantly male workers (Table 1) and for the general population (Table 2). Thus, for chemicals such as PFOA, it is important to consider potential confounding factors such as age and gender when evaluating bioelimination half-lives from biomonitoring data to ensure appropriate application in subsequent toxicokinetic modeling.

5. Conclusions

Perfluorooctanoic acid (PFOA) is a persistent and widely dispersed environmental pollutant that has been detected in biota and humans worldwide. Based on evaluation of two biomonitoring studies of the general population, the intrinsic plasma elimination half-life of PFOA in humans is estimated to be 2.4 years, representing the average of the results from Brede et al. (2.5 years, 95% CI 2.4–2.7) and Bartell et al. (2.3 years, 95% CI 2.1–2.4). The accurate determination of intrinsic chemical elimination half-lives from longitudinal or cross-sectional studies of human blood, plasma or serum requires careful consideration of the magnitude of the observed concentration changes as well as evaluation of the extent of ongoing levels of exposure. Calculation of intrinsic chemical elimination half-life values clarifies the actual rate of metabolism and elimination and permits improved understanding and prediction of the fate of xenobiotic chemicals in humans.

Determination of the bioelimination rate of xenobiotics is a critical component of toxicokinetic modeling and subsequent risk assessments. Failure to account for ongoing exposure results in calculation of biased elimination rates and produces exaggerated estimates of chemical elimination half-lives. Care should be taken in calculating and reporting elimination data to minimize misunderstanding and potential misuse of experimental kinetic results. For some chemicals, factors such as age or gender may impact intrinsic elimination half-life values for specific subpopulations and additional values may be needed to enable accurate toxicokinetic modeling of subpopulations.

Evaluation of elimination kinetics from biomonitoring data without explicitly compensating for the effects of ongoing exposure can lead to speculation involving nonlinear elimination kinetics and novel retention mechanisms, especially when monitored concentrations approach background values (Costa et al., 2009; Yali and Yaqi, 2014). Evaluation of accurate intrinsic elimination rates for PFOA from humans can contribute to improved exposure assessments, more reliable risk assessments and more complete understanding of the behavior of persistent chemicals in the environment. Kinetic equations similar to those described in this study can be developed to differentiate between intrinsic and apparent rates of chemical decline in environmental media such as lakes and soil where input sources occur simultaneously with various elimination mechanisms.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemosphere.2014.07.061.

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