Application of a simplified bioaccumulation model : Estimation of elimination half-lives for PCDD/PCDFs

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Introduction

Elimination half-lives ($t_{1/2}$), representing the time required to reduce the body burden of an organism by half, are an important criterion in hazard assessments of chemicals as they can be seen as an indicator of the potential of a substance to bioaccumulate[1]. For highly lipophilic and recalcitrant substances such as PCDDs and PCDFs, estimating elimination half-lives in humans is quite complicated due to the long time periods required and the many confounding factors. To address these problems, Geyer et al. (2002)[1] proposed the following estimation methods:

$t_{1/2H} = 150 \cdot t_{1/2R}$ [1]

$\log t_{1/2H} = 1.34 \log t_{1/2R} + 1.25$ [2]

where $t_{1/2H}$ and $t_{1/2R}$ are the elimination half-lives for humans and rats respectively.

Another possible approach for estimating elimination half-lives is through the use of physiologically-based pharmacokinetic models[2]. Due to the complexity of these models however, more simplified bioaccumulation models are typically used for exposure assessment estimations. Thus the purpose of this short paper is to derive total elimination rate constants for humans using a simplified bioaccumulation model and compare the model values to the estimates generated by the methods discussed above. Comparisons to other reported values cited by Geyer et al. (2002)[1] will also be made.

Methods

The model applied is based on a terrestrial bioaccumulation model first developed and applied to shrews inhabiting floodplains in the Netherlands[3]. The approach utilized is similar to models published in the scientific literature for aquatic organisms[4], terrestrial organisms[5] and humans[6,7]. Briefly, terms representing uptake and elimination rates are estimated and the change in concentration in humans (C_H, pg wet weight $\cdot$ m^{-3}) over time is then calculated as :

$dC_H / dt = k_{UA} \cdot C_A + k_{UD} \cdot C_D + k_{US} \cdot C_S + k_{UW} \cdot C_W$ – [3]

$(k_{EA} + k_{UE} + k_{FE} + k_{BE} + k_{LA} + k_{MT} + k_{GD} + k_{RD}) \cdot C_H$

where C_A, C_D, C_S, C_W are the concentrations of chemical (pg $\cdot$ m^{-3}) in ambient air, diet, soil and water respectively, k_{UA},k_{UD}, k_{US} and k_{UW} are first-order rate constants (d^{-1}) characterizing uptake from air, diet, ingested soil and water respectively and k_{EA}, k_{UE}, k_{FE}, k_{BE}, k_{LA}, k_{MT}, k_{GD} and k_{RD} are the rate constants (d^{-1}) characterizing elimination via respiratory exchange, urination, defecation, biliary elimination, lactation, metabolic transformation of parent compound and pseudo-elimination related to growth dilution and reproduction. From this equation, the total elimination half-life $t_{1/2}^{ELIM}$ can be estimated as ln(2) / k_{SELIM}, where k_{SELIM} is simply the sum of all elimination rate constants.

As fecal excretion has been shown to be the major mechanism for elimination for highly lipophilic and recalcitrant chemicals[7], only the definition of that rate constant is explicitly discussed in this paper. In the model, fecal elimination is estimated as

$k_{FE} = (G_F * E_D) / (V_H * K_{BF})$ [4]

where G_F is the amount of fecal matter excreted ($m^3 \cdot d^{-1}$), E_D is the dietary uptake efficiciency, V_H is the volume of the organism and K_{BF} is the partition coefficient describing the distribution of chemical between biota and its fecal matter defined as :

$K_{BF} = Z_B / Z_F$ [5]

where Z_B and Z_F are the fugacity capacities of the body and its feces respectively. Following Kelly and Gobas[4], biological matter is viewed as consisting of three phases: (i) lipid (ii) non-lipid organic matter (NLOM) and (iii) water. The fugacity capacity of the body and the feces are thus calculated as :

$Z_{B,F} = (F_L + F_{NLOM} * f_{NLOM}) \cdot K_{OW} + F_W$ [6]

where F_L, F_{NLOM} and F_W are the fraction of lipid, non-lipid organic matter and water in the biological phase (i.e. body or feces) and f_{NLOM} is a proportionality constant relating the sorptive capacity of NLOM to octanol, initially set to 0.035[4].

The rate of fecal excretion (G_F, $m^3\ d^{-1}$) is based on the amount of food consumed (G_D, $m^3\ d^{-1}$) and the digestibility of the diet, which is determined by absorption efficiencies for lipid, NLOM and water (a_L, a_{NLOM}, a_W). Note that these absorption efficiencies also determine the fraction of lipid, NLOM and water in the feces. The final term, E_D was estimated with an empirically derived equation reported by Moser & McLachlan (2001)[8]

$1/E_D = 1.01 + 1.55 \cdot 10^{-9} \cdot K_{OW}$ [7]

Based on this model formulation, total elimination half-lives for lipophilic compounds are largely dependent on the consumption rate (G_D) and composition of the diet, the dietary absorption efficiencies (a_L, a_{NLOM} and a_W), the composition of the human body (F_L, F_{NLOM}, F_W) and K_{OW}. Default values for these parameters and the ranges used to determine the minimum and maximum values in half-life estimates are shown in Table 1.

Table 1 – Default Parameter Values and Associated Ranges

Parameter	Default Value	Range
G_D	1.032 kg $\cdot$ d^{-1}[9]	0.75 – 2 $\cdot$ G_D
a_L	0.98[5]	0.9 – 1
a_{NLOM}	0.75[5]	0.6 – 0.9
a_W	0.95[5]	-
F_L	0.25	0.2 – 0.4
F_{NLOM}	1 - F_L – F_W	-
F_W	0.71 $\cdot$ (1 - F_L)[6]	-

K_{OW} and thus E_D are obviously chemical dependent. Minimum values represent a human with the highest consumption rate (G_D), lowest digestive efficiency and total body fat content while maximum values represent a human with the lowest consumption rate, highest digestive efficiency and total body fat content.

Results and Discussion

Mean estimated elimination half-lives (years) and the range of estimates generated using data for rats reported by Geyer et al. (2002)[1] are shown in Table 2 along with values generated using the simplified bioaccumulation model. Literature values cited by Geyer et al. (2002)[1] are shown in Table 3.

Table 2 – Comparison of Estimated Elimination Half-lives (years)

Congener	log K_{OW}	Geyer I		Geyer II		Model	
		Mean	Range	Mean	Range	Default	Range
2378-TCDD	6.96	7.7	6.2 - 9.7	2.5	1.8 - 3.4	8.5	1.5 - 54.9
12378-PeCDD	7.5	12.7	11.2 - 13.6	4.8	4.1 - 5.3	8.8	1.6 - 57.0
123478-HxCDD	7.94	45.2	34.1 - 64.1	26.5	18.2 - 42.3	9.6	1.7 - 62.4
1234678-HpCDD	8.4	103.2	82.2 - 129.0	80.0	59.0 - 108.0	11.6	2.1 - 75.5
OCDD	8.75	132.3	71.1 - 169.7	111.8	48.6 - 156.0	15.6	2.8 - 101.5

Table 3 – Reported Values for Elimination Half-lives Cited by Geyer et al. (2002)[1]

Congener	Other Reported Values[1]
2378-TCDD	5.8 - 9.7
12378-PeCDD	13.0 - 15.7
123478-HxCDD	8.4 - 26.2
1234678-HpCDD	3.7 - 90
OCDD	6.7 - 50

Estimated values for the elimination half-life of 2,3,7,8-TCDD are similar between Geyer Method I, the default simplified bioaccumulation model and other values cited by Geyer et al.(2002)[1]. For the other congeners, the default simplified bio- accumulation model estimates lie at the lower range of reported values and fall well below the estimates generated by the two Geyer methods. While the bioaccumulation model can be parameterised to produce similar values as the Geyer methods for the higher chlorinated congeners, the values for the lower chlorinated congeners are then greatly overestimated. It is important to note that the model does provide an explanation for two important trends in elimination half-lives described by Geyer et al (2002)[1], namely that half-

lives increase with total body fat content and the lipophilicity (K_{OW}) of the chemical. Furthermore, the model can illustrate how elimination kinetics of aging individuals change due to increasing body fat content and lower consumption (and thus excretion) rates and the corresponding effect on the elimination rate constant (k_{SELIM}). However, for a given individual with fixed body composition, the bioaccumulation model can not produce the nearly 20-40 fold increase in elimination half-lives suggested by the Geyer methods for OCDD compared to TCDD. On the otherhand, it is interesting to note that model estimates of elimination half-life estimates for similarly lipophilic compounds in shrews[2] correspond reasonably well to the observed values for rats cited by Geyer et al (2002)[1].

The purpose of this paper was not to argue that one set of elimination half-life estimates is more "correct" than others, but rather to highlight the differences between estimates of half-lives based on the outlined approaches. While the simplified bioaccumulation model approach permits a dynamic estimation of the elimination rate constant based on physico-chemical properties and dietary, physical and physiological considerations, it does not produce the same relationship between K_{OW} and elimination rate constants suggested by the Geyer methods or some of the other reported data. Possible explanations for this discrepancy include if 1) E_D declines much more rapidly as a function of K_{OW} than suggested by the empirical relationship used or 2) transfer of chemical into the intestinal tract is inhibited compared to transfer out of the intestinal tract (i.e. uptake). Studies of dietary uptake in humans[7,8] do not support these suppositions, although debate regarding mechanisms of intestinal absorption continues[10]. As is discussed by Geyer et al. (2002)[1], elimination kinetics of highly lipophilic compounds are complicated and can be influenced by many biotic and abiotic factors. This short paper is merely meant to contribute to the exploration of these issues, rather than propose definitive conclusions.

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