ELSEVIER

Chemosphere 57 (2004) 745–753

CHEMOSPHERE

www.elsevier.com/locate/chemosphere

The relationship between elimination rates and partition coefficients

S.A.L.M. Kooijman *, T. Jager, B.W. Kooi

Department of Theoretical Biology, Faculty of Earth & Life Sciences, Vrije Universiteit, de Boelelaan 1087, 1081 HV Amsterdam, Netherlands

Received 10 June 2004

Abstract

Rate constants for uptake and elimination of chemicals in organisms are often related to partition coefficients (typically the octanol–water partition coefficient). We show that the well-mixed one-compartment model for toxico-kinetics implies that the elimination rate is inversely proportional to the square root of the partition coefficient. When chemical exchange is limited by diffusion in the boundary layers adjacent to the interface, two-film models are appropriate, which have more complex implications for the relationships between the exchange rates and the partition coefficient. We also show that the popular steady-flux approximation of the two-film model is not a conceptual generalization of the one-compartment model, although it shares the first-order kinetics. We compare the kinetics of a series of models with an increasing number of well-mixed compartments for exchange, such that the two-film model results for an infinite number of compartments. The latter model formulation in terms of partial differential equations, and more in particular its boundary condition at the interface of the two media, is believed to be new. In the steady-flux approximation and in the model with single well-mixed boundary layers and low diffusivities, the elimination rate depends hyperbolically on the partition coefficient. The available data for abiotic systems (SPME fibers) supports a hyperbolic relationship, whereas the data for aquatic biota are less discriminating between a hyperbolic or a square root relationship with the partition coefficient. The daphnia data showed less scatter than the fish data, possibly due to the small variance in body sizes, since elimination rates are inversely proportional to body length. The square root relationship fitted these data best.

Keywords: Elimination rate; Partition coefficient; One-compartment model; Two-film model; Square root relationship; Transport

1. Introduction

Knowledge about elimination rates in the context of (eco)toxicological research is of importance to design experiments on toxico-dynamical properties of the compound, and to predict body residues under time-varying exposure. These rates depend on a number of factors, such as the temperature and the size of the organism. If elimination is proportional to the internal concentration, so to the amount of the compound per volume, and chemical exchange with the environment is proportional to surface area, the elimination rate should be proportional to the ratio of the surface area and the volume of an organism. If the organism does not change in

* Corresponding author. Tel.: +31 20 444 7130; fax: +31 20 444 7123.
E-mail address: bas@bio.vu.nl (S.A.L.M. Kooijman).
URL: http://www.bio.vu.nl/thb/ (S.A.L.M. Kooijman).

0045-6535/$ - see front matter
doi:10.1016/j.chemosphere.2004.08.005

shape during growth, the elimination rates should be inversely proportional to a length measure (Kooijman, 2000), i.e. to the cubic root of body weight. If we compare different organisms, we should therefore correct for differences in size.

This paper discusses the relationship between the elimination rate and the partition coefficient. This partition coefficient depends on the chemical composition of the organism, so on its nutritional status, which might vary in time. Octanol is frequently taken to be a chemical model for 'typical' animal lipids. Estimates of the octanol–water partition coefficients, P_{ow}'s, are usually available, and sometimes elimination rates of physiologically related compounds are known from other experiments. Prior estimates for the elimination rate of the compound under study can be used to estimate the exposure time that is required to achieve a close to complete saturation of the compound in the tissues. This is also of importance for experiments to quantify toxic effects of the compound, because these effects also depend on the concentrations in the tissues (Kooijman, 1981; McCarty and Mackay, 1993).

The standard approach to find a prior estimate for the elimination rate, given a set of elimination rates of physiologically related compounds, is to use quantitative structure activity relationships (QSARs), which generally boils down to the application of the allometric model $k_e = kP_{ow}^{\alpha}$, or $\ln k_e = \ln k + \alpha \ln P_{ow}$, where k_e is the elimination rate, while the reference rate k and the exponent α are obtained from linear regression of the log-transformed partition coefficient and elimination rate data. The model lacks any theoretical underpinning and suffers from the problem that a reliable regression requires a large number of data points, which puts some doubt on the assumption that all these compounds have physiologically related uptake and elimination mechanisms.

The literature on theoretical prediction for the relationship(s) between elimination rates and partition coefficients is somewhat confusing. Some references state that the uptake rate has an optimum with P_{ow} (Thomann, 1989), others state that the uptake and the elimination rate depend hyperbolically on P_{ow} (Gobas and Opperhuizen, 1986; Sijm and Van der Linde, 1995), while others state that the uptake rate is proportional to $\sqrt{P_{ow}}$, while the elimination rate is proportional to $1/\sqrt{P_{ow}}$ (Kooijman, 2000). The purpose of this paper is to present a systematic discussion of the topic, and to give a new, and extended, derivation of the basic result that one-compartment models for kinetics imply that the elimination rate is proportional to $1/\sqrt{P_{ow}}$. We then compare the implications for the popular one- and two-film models, which are not one-compartment models. After discussing the connections between film and one-compartment model, we test predictions against experimental data. See Table 1 for the symbols.

2. 1,1- and 1-compartment models

We first consider a 1,1-compartment model, where we think of a cylinder filled with two homogeneous media that do not mix, and a compound that can move freely from one medium to another across the interface with surface area S (see Fig. 1). The total number of molecules of the compound is taken to be constant, contrary to a one-compartment model where the concentration in the environment of the compartment is taken to be constant or a specified forcing function of time. N_i molecules are in medium i of constant volume $\mathscr{V}_i$, with $i = 0, 1$, so the concentration is $c_i = N_i/\mathscr{V}_i$. We introduce a one-dimensional spatial axis, perpendicular on the plane of the interface between the two media, and do not correct for a possible curvature of this interface; the depth of medium i is $\mathscr{L}_i = \mathscr{V}_i/S$. The standard 1,1-compartment model amounts for $j = 1 - i$ to

$$\frac{\mathrm{d}}{\mathrm{d}t}c_i = \mathscr{L}_i^{-1}(v_{ji}c_j - v_{ij}c_i) \qquad \text{or} \qquad \frac{\mathrm{d}}{\mathrm{d}t}N_i = k_{ji}N_j - k_{ij}N_i \tag{1}$$

where v_{ij} is the exchange velocity (i.e. a mass transfer coefficient) and $k_{ij} = v_{ij}/\mathscr{L}_i$ the exchange rate of the compound. At equilibrium we have that $\frac{c_i}{c_j} = \frac{v_{ji}}{v_{ij}} = \frac{\mathscr{L}_j}{\mathscr{L}_i}\frac{k_{ji}}{k_{ij}} = P_{ij}$, where P_{ij} is called the partition coefficient.

Table 1
List of frequently used symbols

Symbol	Dim	Interpretation	Symbol	Dim	Interpretation
t	t	Time	h_i, k_i, k_e, k_{ij}	t^{-1}	Rate
v_i, v_{ij}	lt^{-1}	Velocity	d_i	l^2t^{-1}	Diffusivity
c_i, c_{ij}	$\#l^{-3}$	Concentration	n_i, n_{ij}	$\#l^{-1}$	Density
$\mathscr{L}_i$	l	Depth of mixed bulk	l_i	–	Scaled length
L_i, L_{ij}	l	Depth of boundary (sub)layer	$\mathscr{V}_i$	l^3	Volume of mixed bulk
S	l^2	Surface area	V_i, V_{ij}	l^3	Volume of boundary (sub)layer
i, j, n	#	Number	N_i, N_{ij}, M	#	Amount
P_{ij}	–	Partition coefficient			

The symbols in the dimension specification stand for # number, t time, l length. Vectors and matrices are printed in bold face.

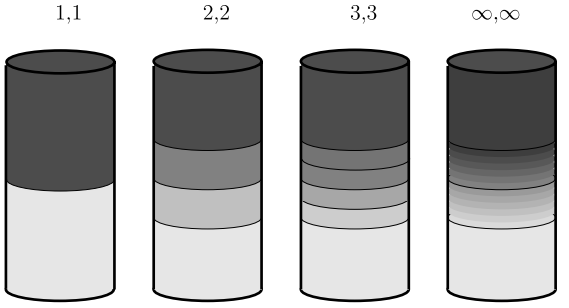

Fig. 1. The sequence of physical systems that we study in this paper, called n,n-compartments. The medium 0 is confined to the upper compartment in the cylinder, medium 1 to the lower one; they cannot cross the thin line that separates them, while the compound can but with possibly different concentration-specific rates. The compound can also cross the very thin lines within the media, but with the same specific rates. Starting from the simplest situation at the left, $n = 1$, the system converges for $n = 2, 3, \ldots$ to the two-film system at the right in which we have continuous concentration gradients in the layers on each side of the interface between the media.

To simplify the notation, we write x for the partition coefficient P_{01} and try to find how the elimination rate depends on x. Let us say that the elimination rate k_{01} is some function f of x, i.e. $k_{01} \propto f(x)$, which we want to know. We solve the problem in two steps.

We first demonstrate that the partition coefficient can be written as a quotient of two similar terms, one depending only on i, and the other only on j. For this purpose we suppose that an extremely thin slice separates two media; the compound can cross the slice freely. The assumption of well-mixed compartments, which is basic to one-compartment models, excludes any concentration gradients. If M denotes the number of molecules in the slice, we get

$$\frac{\mathrm{d}}{\mathrm{d}t}N_i = h_i M - k_i N_i \tag{2}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}M = k_i N_i + k_j N_j - h_+ M \tag{3}$$

where the hazard rate h_i quantifies the specific escape rate from the slice to medium i, while $h_+ = h_i + h_j$. We have $k_i = v_i/\mathscr{L}_i$, where the velocity v_i does not depend on the depth $\mathscr{L}_i$ of medium i. On each side of the slice, the compound cannot 'feel' the presence of the other medium; only in the slice can the compound 'sense' both media, k_i does not depend on any property of medium j. We have that M is very small with respect to the total amount of molecules, implying that $h_i \gg k_i$ and that the dynamics of M is fast with respect to that of N_i.

Suppose that M is in pseudo-equilibrium, so $M^* = k_i N_i/h_+ + k_j N_j/h_+$. Substitution of this result in (2) gives

$$\frac{\mathrm{d}}{\mathrm{d}t}N_i = N_j k_j h_i/h_+ - N_i k_i h_j/h_+ \tag{4}$$

From (1) it follows that $k_{ij} = k_i h_j/h_+$ or $v_{ij} = v_i h_j/h_+$. The exchange rate, therefore, depends on the properties of medium i and j. The partition coefficient is

$$P_{ij} \equiv \frac{c_i^*}{c_j^*} = \frac{\mathscr{L}_j}{\mathscr{L}_i}\frac{N_i^*}{N_j^*} = \frac{\mathscr{L}_j}{\mathscr{L}_i}\frac{k_j}{k_i}\frac{h_i}{h_j} = \frac{v_j}{v_i}\frac{h_i}{h_j} = \frac{g_i}{g_j}$$

with $g_i = h_i v_i^{-1}$. The partition coefficient can thus indeed be written as a ratio of two similar terms, each depending on a single medium only. The term g_i is the value of some function of properties of the compound and medium i that we could quantify with a variable y_i, for instance, while g_j is the value of that same function, but now applied to medium j rather than i. If the elimination rate can be written as $k_{ij} \propto f'(y_i)/f'(y_j)$, we have the condition $f(x) = 1/f(1/x)$. This means that the unknown function f belongs to the class of the power functions: $f(x) = x^\alpha$, for some arbitrary value of the coefficient α (at this moment in our reasoning).

The second step in our derivation is the use of the skew-symmetry argument, which boils down to interchanging media. The rationale is that our choice which of the media we label with 0 or 1 has been fully arbitrary. The result of how the elimination rate depends on the partition coefficient should not depend on this choice. Given that $k_{01} \propto f(x)$, we know that the uptake rate $k_{10} \propto f(1/x)$, so we have that $\frac{f(1/x)}{f(x)} = x$. This condition allows for a large class of functions, but in combination with our previous condition $f(1/x) = 1/f(x)$, it leads to a unique solution, namely $f(x)^{-2} = x$ or $f(x) = x^{-1/2}$.

The final result is that

$$k_{ij} \propto v_{ij} \propto 1/\sqrt{P_{ij}} \quad \text{and} \quad k_{ji} \propto v_{ji} \propto \sqrt{P_{ij}}$$

which relates rate parameters to a steady state. The argument for these relationships are all basic to the one-compartment model, apart from the assumption that the rates *can* be written as a function of the partition coefficient, which is by no means self evident. Notice that the temperature, mixing rates, molecular size of the compound, surface area of exchange, and other modifying factors affects the proportionality constants of the rates, not how they depend on the partition coefficient.

If medium 0 represents some organism, and medium 1 the aquatic environment in which the concentration is constant at level c_1, the model reduces to 1,0-compartment model, better known as the 1-compartment model

$$\begin{aligned} c_0(t) &= c_0(0)\exp\{-k_{01}t\} + c_1 P_{01}(1 - \exp\{-k_{01}t\}) \\ &= c_0(0)\exp\{-k_{01}t\} \quad \text{for } c_1 = 0 \\ &= c_1 P_{01}(1 - \exp\{-k_{01}t\}) \quad \text{for } c_0(0) = 0 \end{aligned}$$

The rate k_{01} now has the interpretation of the elimination rate. The time we have to wait to saturate the tissue

of an uncontaminated organism to a fraction x of the ultimate level is $t_x = -k_{01}^{-1}\ln(1-x)$. It is independent of the concentration in the environment and of the uptake rate, and equals the time required to reach a fraction $1-x$ of the original concentration in the tissue if an exposed organism experiences an uncontaminated environment. We mention these trivialities in preparation of further discussions.

The one-compartment model is obviously a very simple one, in which both media are well-mixed. We will now study an extension of the model, in which the media are no longer well-mixed.

3. Film models

Film models are widely used in environmental chemistry. They are popular because they account for spatial structure of transport in a very simple, yet appealing way, but they suffer from the problem that the films, i.e. the non-mixed layers, can typically not be identified in a direct way. This complicates the link between model predictions and data.

Suppose that the media are now separated by rather thin layers of thickness L_i, see Fig. 1. We will use the notation that the depth of the layer $L = 0$ at the mixed bulk for both media, and $L = L_i$ at the interface. The volume between lengths L_a and L_b is given $V(L_a, L_b) = (L_b - L_a)S$, in both media. The density n of the compound in layer i relates to the number of molecules as $N_i(L_a, L_b, t) = \int_{L_a}^{L_b} n_i(L,t)\mathrm{d}L$; we have concentration $c_i(L_a, L_b, t) = N_i(L_a, L_b, t)/V(L_a, L_b)$. If the bulk has depth $\mathscr{L}_i$, there are $N_i = n_i(0)\mathscr{L}_i$ molecules in the bulk, which makes that the total amount of molecules in medium i is $N_i^+ = n_i(0)\mathscr{L}_i + N_i(0, L_i)$. The volume of the well-mixed medium is $\mathscr{V}_i = \mathscr{L}_i S$, and of the total medium is $V_i^+ = (\mathscr{L}_i + L_i)S$, so the (mean) concentration is $c_i^+ = N_i^+/V_i^+$. The concentration in the bulk is $c_i = c_i(0) = n_i(0)/S$. We need this notation to compare the different models that we will discuss.

Assuming that the initial densities $n_i(L,0)$ are given such that the boundary conditions in (7) apply, the dynamics for the densities is given for $i = 1 - j$ by partial differential equations (pde's)

$$0 = \frac{\partial}{\partial t} n_i(L,t) - d_i \frac{\partial^2}{\partial L^2} n_i(L,t) \quad \text{for } L \in (0, L_i) \tag{5}$$

with boundary conditions at $L = 0$ for $v_i = d_i/L_i$

$$0 = \frac{\partial}{\partial t} n_i(0,t) - v_i \frac{\partial}{\partial L} n_i(0,t) \tag{6}$$

and boundary conditions at $L = L_i$

$$0 = v_{ji} n_j(L_j,t) - v_{ij} n_i(L_i,t) + d_i \frac{\partial}{\partial L} n_i(L_i,t) \tag{7}$$

The latter boundary conditions are believed to be new, despite the popularity of the film-models.

For increasing diffusivity's d_i, and/or decreasing thickness of the non-mixed layers L_i, this two-film model reduces to the 1,1-compartment model of the last section. This reduction will be discussed in the following sections. So it is an extension of the same ideas behind the 1,1-compartment model, but now accounts for lack of mixing in the boundary area.

This model has rather complex properties, therefore, we will study simplifications of it.

3.1. Steady-flux approximation

Suppose now that transport in the films is steady, i.e. the density profiles do not change in time, so $\frac{\partial}{\partial t} n_i(L,t) = 0$. Suppressing argument t, we then have according to (5) that

$$0 = \frac{\mathrm{d}^2}{\mathrm{d}L^2} n_i(L) \quad \text{for } L \in (0, L_i)$$

The density profiles in the films are thus linear:

$$\frac{\mathrm{d}}{\mathrm{d}L} n_i(L) = (n_i(L_i) - n_i(0))/L_i$$

The mass balance across the bi-film gives $L_i \frac{\mathrm{d}}{\mathrm{d}t} n_i(0) = -L_j \frac{\mathrm{d}}{\mathrm{d}t} n_j(0)$, which leads via (6) to $(n_j(L_j) - n_j(0))v_j = -(n_i(L_i) - n_i(0))v_i$. Substitution of this result in (7) gives $n_i(L_i)$ as a weighted sum of $n_i(0)$ and $n_j(0)$. Back-substitution in (6) finally leads to the first-order kinetics for the bulk densities $\frac{\mathrm{d}}{\mathrm{d}t} n_i(0) = k_e(P_{ij} n_j(0) - n_i(0))$ with elimination rate

$$k_e = k_i(1 + P_{ij} v_i/v_j - v_i/v_{ij})^{-1}$$

for $v_i v_j < v_{ij} v_j + v_{ji} v_i$. The restriction of this approximation is that the change in bulk densities n_i is sufficiently small to allow the transport flux in the bi-film to be steady and that transport within the film is strictly limiting; this is not necessarily true. If the transport within the bi-film is very slow, relative to the exchange velocities across the interface, $v_i v_j \ll v_{ij} v_j + v_{ji} v_i$, the elimination rate simplifies to $k_e \simeq k_i(1 + P_{ij} v_i/v_j)^{-1}$, while $n_i(L_i) \simeq P_{ij} n_j(L_j)$. Boundary condition (7) shows that this can only be a crude approximation indeed, because a gradient is required to drive diffusive transport, and the concentration jump across the interface only equals the partition coefficient in absence of a gradient in the films.

The time we have to wait to saturate the tissue of an uncontaminated organism to a fraction x of the ultimate level is $t_x = -k_e^{-1}\ln(1-x)$. Fig. 2 illustrates how this time relates to the P_{ow}. We see that the elimination rate k_e is now a hyperbolic function of the partition coefficient. This result is reported by Schwarzenbach et al. (1993) for air–water exchange, by Flynn and Yalkowsky (1972) for artificial membranes, and by Gobas and Opperhuizen (1986) for fish. For low P_{ow} values, the

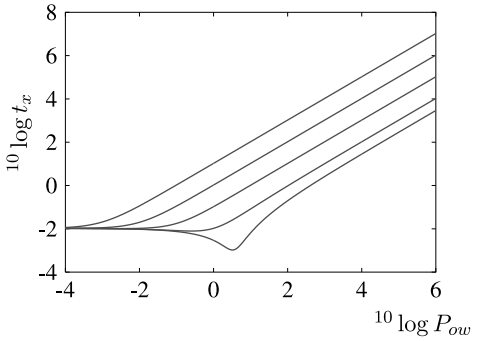

Fig. 2. A log–log plot of the time to reach an x-level saturation in the tissues of an organism exposed in an environment with a constant concentration of a compound in a two-film model, using the steady-flux approximation. The curves correspond with different values of the velocity v_1; the upper curve has the lowest velocity. Parameters: $v_0 = 1$, $v_1 = 0.001$, 0.01, 0.1, 1, $3.6\,\mathrm{mm\,h^{-1}}$. $v_{01} = P_{\mathrm{ow}}^{-1/2}$, $v_{10} = P_{\mathrm{ow}}^{1/2}$, $k_0 = 10\,\mathrm{h^{-1}}$, $x = 0.1$. Notice that the $v_1 = 3.6\,\mathrm{mm\,h^{-1}}$ is close its maximum value in this parameter combination to ensure positive elimination rates; the steady-flux approximation is probably very poor in this situation.

elimination rate hardly depends on the P_{ow} and for large values it is inversely proportional to P_{ow}. As a consequence, the opposite holds for the uptake rate. The result of Thomann (1989) is largely consistent with this relationship, if applied to the proper range of P_{ow} values. Notice that this reasoning does not make use of the considerations for how the exchange rates k_{ij} depend on P_{ij} as presented in the earlier section; this is because they do not occur independently in this steady-state flux model, but only in combination as a ratio in the form of P_{ij}.

The steady-flux approximation of two-film model has a one-film model as special case, where e.g. $L_j \to 0$ or $v_j \to \infty$. The elimination rates then reduces to $k_{\mathrm{e}} = k_i(1 - v_i/v_{ij})^{-1}$, and we must have that $v_i < v_{ij}$. Since $v_{ij} \propto 1/\sqrt{P_{ij}}$, this approximation is only valid in a limited range of P_{ij} values, depending on the value of v_i.

This illustrates a serious problem with this steady-flux approximation: contrary to the full pde formulation, we cannot reduce this approximation in a smooth way to the well-mixed special case of a one-compartment model. If we would increase the diffusivities d_i and/or reduce the thickness of the non-mixed layers L_i, we are forced to increase the exchange rates k_{ij} as well to ensure that the transport in the layers is still in pseudo-steady-state. In other words: the dynamics of the system disappear, and the whole system equilibrates instantaneously. We will see that k_{01} and k_{10} occur independently in other approximations of the two-film pde model that do not suffer from this problem. The steady-flux approximation is popular in situations where the bulk volumes are infinitely large and represent the ocean and the atmosphere, for instance. It than becomes a reasonable assumption to take a constant flux from one medium into the other, without changes in the bulk concentrations. This application is quite different from that in toxico-kinetics, where one medium represents an initially uncontaminated fish, and the other an aquarium with a compound, and we study the toxico-kinetics and effects in transient states.

3.2. 2,2- and 2-compartment approximations

In this approximation we assume that the layers adjacent to the interface are well-mixed and write N_{i1} for the amount in the boundary layer of medium i, and N_i for the amount in the bulk of medium i (see Fig. 1). The volume of the layer is V_{i1} and of the bulk $\mathscr{V}_i$, which makes that the concentration in the layer is $c_{i1} = N_{i1}/V_{i1}$ and in the bulk $c_i = N_i/\mathscr{V}_i$. The total amount in medium i is $N_i^+ = N_i + N_{i1}$, the total volume is $V_i^+ = \mathscr{V}_i + V_{i1}$, and the total (mean) concentration $c_i^+ = N_i^+/V_i^+$. The set of pde's is now approximated by the linear ordinary differential equations (ode's) for $k_i = v_i/L_i$ and $l_i = L_i\mathscr{L}_i^{-1}$: $\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{c} = \boldsymbol{k}\boldsymbol{c}$ with

$$\boldsymbol{c} = \begin{pmatrix} c_0 \\ c_{01} \\ c_{10} \\ c_1 \end{pmatrix} \quad \text{and}$$

$$\boldsymbol{k} = \begin{pmatrix} -k_0 l_0 & k_0 l_0 & 0 & 0 \\ k_0 & -k_0 - k_{01} & k_{10} & 0 \\ 0 & k_{01} & -k_1 - k_{10} & k_1 \\ 0 & 0 & k_1 l_1 & -k_1 l_1 \end{pmatrix}$$

This linear system can be integrated explicitly, with solution $\boldsymbol{c}(t) = \exp\{\boldsymbol{k}t\}\boldsymbol{c}(0)$.

For large k_0, the model for N_0^+ reduces to the one-compartment model, just as the pde model, for which this model is an approximation. The link between this 2,2-compartment model and the two-film pde model is discussed in the next subsection.

In order to compare this model with the one-compartment one, we again study the time t_x we have to wait to saturate the tissue of a uncontaminated organism to a fraction x of the ultimate level. This study has to be done numerically, and Fig. 3 summarizes the results. The smallest rate dominates the waiting time. For large P_{ow}, this is the elimination rate, since the diffusivity does not depend systematically on P_{ow}. The figure shows that the second film acts as an extra resistance, which becomes stronger for increasing P_{ow}. While the one-film model has slope 0.5 in the linear sections, the slope is 1 for the two-film model at low diffusivities, and 0.5 for large ones. For low diffusivities, the relationship is similar to the one we found for the steady-flux approximation (i.e. hyperbolic). The results for the two-film model clearly show that we can smoothly go from a hyperbolic relationship (transport dominated by

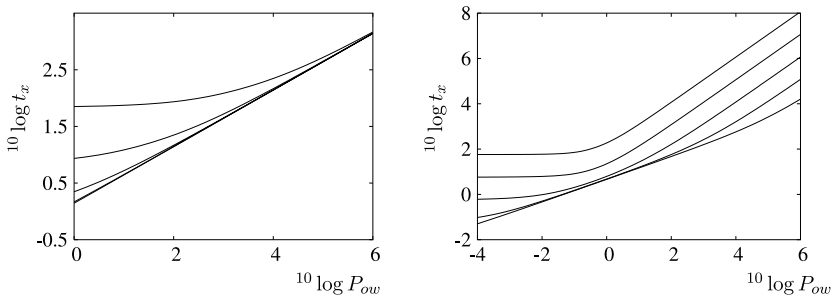

Fig. 3. A log–log plot of the time to reach an x-level saturation in the tissues of an organism exposed in an environment with a constant concentration of a compound with a single film (left) and a double film (right). The curves correspond with different values of the diffusivity in a two-compartment model; the upper curve has the lowest diffusivity. Parameters: $l_0 = 1$, $k_{01} = P_{ow}^{-1/2}$, $k_{10} = P_{ow}^{1/2}$, $k_0 = 0.01, 0.1, 1, 10, 100\,\mathrm{h}^{-1}$ (left), $k_0 = k_1 = 0.04, 0.4, 4, 40, 400\,\mathrm{h}^{-1}$ (right), $x = 0.1$. Notice that the one-film model has slope 0.5, while the two-film model has slope 1 in the linear sections for low diffusivities and high partition coefficients (i.e. low elimination rates), and 0.5 for large diffusivities.

diffusion in the film) to a square-root relationship (transport dominated by exchange across the interface), by changing the parameters of the system.

3.3. n,n-compartment approximations

We can partition the single mixed-layers of the 2,2-compartment model into $2,3,\ldots,n$ layers. We write $V_{ij} = L_{ij}S$ for the volume, and L_{ij} for the depth of sub-layer j in medium i, with $j = 1,2,\ldots,n$. For the sake of notational simplicity, we here take the numbers of sub-layers equal in both media and choose all sub-layers in each medium of equal depth, which gives $L_{ij} = L_i/n$. Both V_{ij} and L_{ij} decrease inversely proportional to n if the depth of the (total) boundary layer $L_i = \sum_{j=1}^{n} L_{ij}$ is taken to be constant. The vector of concentrations and the matrix of coefficients become for $k_i = v_i/L_i$ and $l_i = L_i\mathscr{L}_i^{-1}$

$$\boldsymbol{c} = (\,c_0 \quad c_{01} \quad \cdots \quad c_{0n} \quad c_{1n} \quad \cdots \quad c_{11} \quad c_1\,)^{\mathrm{T}}$$

and

The first item to discuss is how the values for rates k_i' and k_{ij}' and the scaled length l_i' relate to each other for different choices of the number of sub-layers n. The mean residence time of a molecule in the (total) boundary layer should not depend on the number of sub-layers. By requiring $k_i' = (n-1)^2 k_i$ and $k_{ij}' = (n-1)k_{ij}$ and $l_i' = l_i/(n-1)$ for $n = 2,3,\ldots,$ we achieve that an increase of n increases the level of detail of the model, without affecting the overall properties.

By increasing the number of sub-layers $n \to \infty$, while decreasing the depth of each sub-layer $\mathrm{d}L$ such that the depth of the non-mixed layer $L_i = (n-1)\mathrm{d}L$ is constant, this set of ode's converges to the pde model, with the concentration in sub-layer j becomes the surface area-specific density: $c_{ij}(t) \to n_i(L_i j/n, t)/S$ for $j = 1,\ldots,n$, and $k_i \to d_i L_i^{-2}$ and $k_{ij} \to v_{ij} L_i^{-1}$.

Numerical analysis shows that the increase of the number of layers does not have a large quantitative effect, see Fig. 4.

$$\boldsymbol{k} = \begin{pmatrix}
-k_0'l_0' & k_0'l_0' & & & & & & & & & \mathbf{0} \\
k_0' & -2k_0' & k_0' & & & & & & & & \\
 & \ddots & \ddots & \ddots & & & & & & & \\
 & & k_0' & -2k_0' & k_0' & & & & & & \\
 & & & k_0' & -k_0' - k_{01}' & k_{10}' & & & & & \\
 & & & & k_{01}' & -k_1' - k_{10}' & k_1' & & & & \\
 & & & & & k_1' & -2k_1' & k_1' & & & \\
 & & & & & & \ddots & \ddots & \ddots & & \\
 & & & & & & & k_1' & -2k_1' & k_1' & \\
\mathbf{0} & & & & & & & & k_1'l_1' & -k_1'l_1'
\end{pmatrix}$$

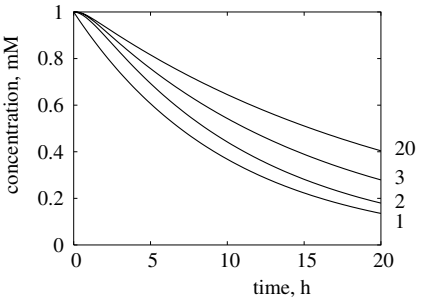

Fig. 4. The time trajectory of the concentration in the bulk $c_0(t)$, for $n = 1, 2, 3, 20$ compartments in medium 0 and no compartments in medium 1, while the concentration in the medium 1 is zero, $c_1 = 0$. The diffusivities are $k_0 = 0.1(n-1)^2 h^{-1}$, while the scaled length $l_0 = 1/(n-1)$. Notice that for $n = 1$ we do not have a diffusion layer and the value for the diffusivity and scaled length are irrelevant; the bulk then eliminates exponentially.

4. Tests against experimental data

In this section we will compare the most extreme simplifications of the pde model to experimental data; the one-compartment model of Section 2 and the two-film steady-flux model of Section 3.1. First, it must be stressed that even though relationships between rate constants and P_{ow} are most abundant in the literature and convenient, the theory is based on the partition coefficient in the actual system studied. This implies that for aquatic organisms, rate constants must be related to the bioconcentration factor (BCF), which is of course itself related to P_{ow}. The two-film steady-flux model results in a hyperbolic relationship between the rate constants and the partition coefficients, whereas in the one-compartment model the uptake rate is proportional to the square root of the partition coefficient, while the elimination rate is inversely proportional to this square root.

The two-film steady-flux model does fit experimental data for steady-state fluxes across a synthetic membrane (Flynn and Yalkowsky, 1972). Results for a non steady-state abiotic system are shown in Fig. 5, where data for uptake and elimination rate constants in solid-phase micro-extraction (SPME) fibers are plotted against the fiber–water partition coefficient (data from Vaes et al., 1996; Verbruggen et al., 2000). In this simple chemical system, the two-film model is clearly superior to the one-compartment model, as the change in diffusion limitation from the hydrophobic phase to the water phase is prominent with increasing partition coefficient. Even though the assumption of a steady-state flux across the interface is violated (the concentration in the fiber obviously changes in time), the model still provides an adequate description of the process.

For chemical exchange between water and organisms, the situation seems to be different. Not only is the assumption of a steady-state flux violated, the identification of the layers and the transport in these layers is unclear. Nevertheless, several authors propose to use a derivation from the two-film steady-flux model for fish (Gobas and Opperhuizen, 1986; Sijm and Van der Linde, 1995), although the data provided by these authors provide little experimental support for this model. The two-film steady-flux model predicts that the elimination rate decreases with hydrophobicity according to a slope of -1 (on log–log scale) in the upper range of P_{ow} values (which appears to be the main area of interest for ecotoxicologists). However, in the literature, widely varying slopes are reported, but generally between -0.5 and -1. The problem with most of these regressions is that P_{ow} is used as the partition coefficient whereas BCF is the relevant partition coefficient in the system.

We here re-analyse data for various fish species taken from Connell and Hawker (1988), spanning a wide range of $\log P_{ow}$ values (2.5–10). The spread in the data is quite large, owing to the combination of different experiments and different fish species. On inspection of the residual sum-of-squares, the one-compartment model performs somewhat better than the two-film steady-flux model (Fig. 5). For *Daphnia pulex* (data collected by Hawker and Connell (1986)), the data are limited and variation is considerable, but the data show a better correspondence to the one-compartment model than to the two-film steady-flux model. The last data set is reported by Sijm and Van der Linde (1995), consisting of data for fathead minnows *Pimephales promelas* at different body sizes. Since body size affects the rate constants, we corrected these values assuming that the rates are proportional to volumetric length^{-1} (where this length is taken as the third root of body weight, assuming a specific density of $1\,g\,cm^{-3}$). For these data, the fit of the two-film model is slightly better than for the one-compartment model.

Hawker and Connell (1985, 1986) related the elimination rate k_e to P_{ow} and found $k_e = 8.851 P_{ow}^{-0.663}$ for fish, $k_e = 113 P_{ow}^{-0.507}$ for *Daphnia pulex* and $k_e = 9.616 P_{ow}^{-0.540}$ for molluscs. The proportionality factor is inversely proportional to the volumetric length of the animal (see above), which explains the wide range of values. The results for daphnids are most reliable, because they have all the same body size, in this case, which suggests that $k_e \propto 1/\sqrt{P_{ow}}$.

In summary, the data for the SPME fibers clearly support the two-film steady-flux model; the logarithms of the uptake and elimination rates have non-linear relationships with the log of the partition coefficient. For the fish and Daphnia data, discrimination between both models is hampered by the poor data quality (which may be expected when dealing with living

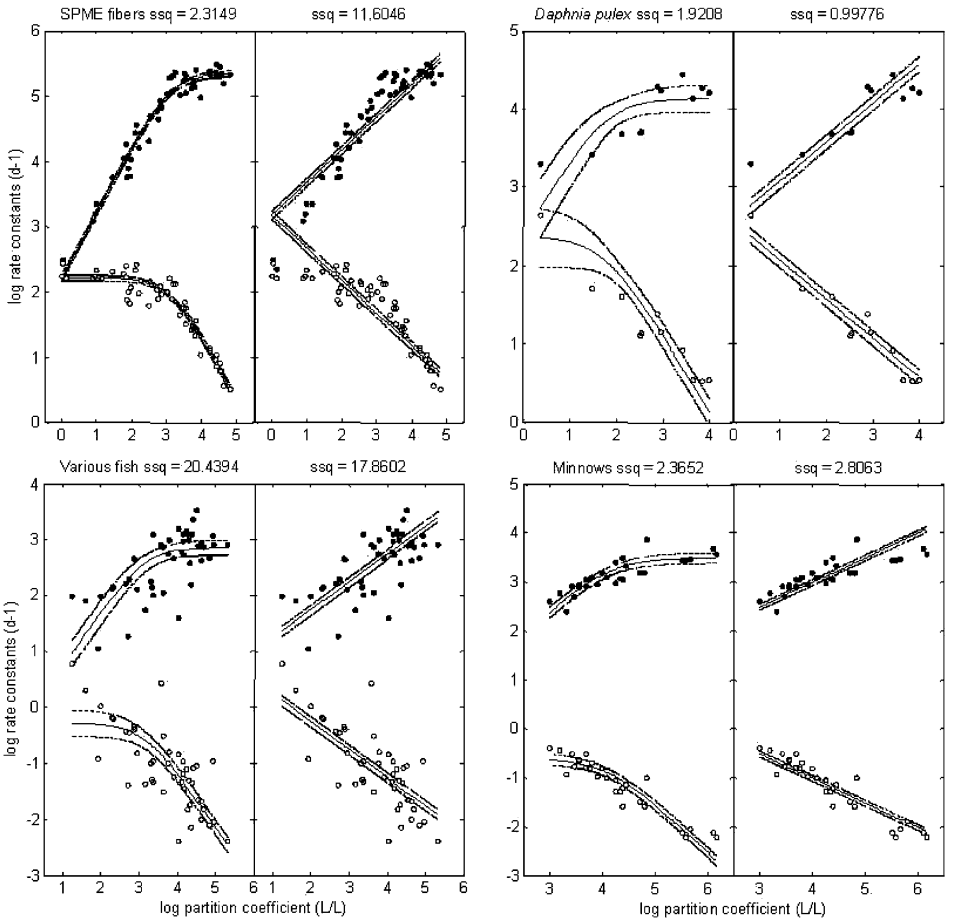

Fig. 5. Comparisons between experimental data and model results. Four data sets are shown, plotting the rate constants (elimination open symbols, uptake closed symbols) versus the partition coefficient. Each data set is shown twice, fitted with a hyperbolic (left panel) or a square root (right panel) relationship. 95% confidence bounds are shown as broken lines.

organisms), and a scarcity of data for hydrophilic compounds; the one-compartment model fits well, given the scatter in the data. The results from these data sets therefore imply that diffusion does not clearly limit transport in daphnia and fish, which might be due to relatively high values of the diffusivities and/or to the relatively small thickness of the non-mixed layers. Their swimming activity might reduce the thickness of the non-mixed layer in the water, for instance, while transport via blood might reduce the thickness of the non-mixed layer in the organism. The scatter in the data obviously does not allow firm conclusions here.

5. Discussion

Contrary to the partition coefficient (which is a concept that is independent of a particular choice of model), the elimination rate is the name of a particular parameter of the one-compartment model. Many alternative models and extensions of the one-compartment model have more than one rate parameter, which make that *the* elimination rate is no longer defined. We here circumvented the problem by focusing on the waiting time for the concentration in the bulk to hit a threshold value relative to the one in steady state. This is practical in the context of experimental design of bioassays for ecotoxicity.

As long as the one-compartment model applies, the strength of the application of the result that $k_e \propto 1/\sqrt{P_{ow}}$ is that if we know the P_{ow} of the compound and the k_e^* and P_{ow}^* of a physiologically related compound, the estimate of the elimination rate is $k_e = k_e^* \sqrt{P_{ow}/P_{ow}^*}$. So we need to know the properties of a single reference compound only, which allows us to be more strict in the condition that the compound is physiologically related and only differs in the P_{ow} value. The square root relationship can be seen as a special case of the allometric model that is mentioned

in the introduction for fixed scaling exponent $\alpha = -1/2$; treating this exponent as a regression parameter makes little physical sense. Moreover, we need more data for this regression.

We showed that transport resistance in the media causes deviations from the square-root relationship. In a mono-film the waiting time is again proportional to $\sqrt{P_{ow}}$ for large P_{ow} values. At low P_{ow} values, however, it is less steeply dependent on P_{ow}, because the transport in the film then restricts the flux. In a bi-film the waiting time is proportional to P_{ow}, rather than to $\sqrt{P_{ow}}$; the second film acts as an extra resistance for transport, which becomes stronger with the P_{ow}. In the extreme situation of a steady flux, we can see this relationship analytically.

In contrast to the data for SPME fibers, the experimental data on toxico-kinetics in fish and daphnids that we analysed the provided little support for the bi-film model, and the elimination rate were found to be largely consistent with square-root relationships. However, the data provided insufficient detail to choose one particular model over the other.

The models considered in this paper are an extreme simplification of the very complex phenomena in nature. The one-compartment model can be, and has been, extended into many more directions other than the inclusion of films. The most popular and classic one is in multi-compartments in pharmacology, where the compartments represent body parts, see e.g. Jacquez (1972). Other extensions include dilution by growth, changes in lipid content, several uptake and elimination routes that are linked to metabolic performance, metabolic transformation, etc. See Kooijman (2000) for an overview. Nevertheless, one-compartment models do capture the main features of toxico-kinetics, and a better understanding of this simple basic model does serve its extensions.

Acknowledgments

We would like to thank Dik van de Meent and José Ferreira for helpful and stimulation discussions. This research was supported by the Netherlands Technology Foundation STW, applied science division of NWO and the technology programme of the Ministry of Economic Affairs (WEB.5509).

References

Connell, D.W., Hawker, D.W., 1988. Use of polynomial expressions to describe the bioconcentration of hydrophobic chemicals by fish. Ecotox. Environ. Safety 16, 242–257.

Flynn, G.L., Yalkowsky, S.E.L., 1972. Correlation and prediction of mass transport across membranes i: Influence of alkyl chain length on flux-determining properties of barrier and diffusant. J. Pharm. Sci. 61, 838–852.

Gobas, F.A.P.C., Opperhuizen, A., 1986. Bioconcentration of hydrophobic chemicals in fish: relationship with membrane permeation. Environ. Tox. Chem. 5, 637–646.

Hawker, D.W., Connell, D.W., 1985. Relationships between partition coefficient, uptake rate constant, clearance rate constant, and time to equilibrium for bioaccumulation. Chemosphere 14, 1205–1219.

Hawker, D.W., Connell, D.W., 1986. Bioconcentration of lipophilic compounds by some aquatic organisms. Ecotox. Environ. Safety 11, 184–197.

Jacquez, J.A., 1972. Compartment Analysis in Biology and Medicine. Elsevier, Amsterdam.

Kooijman, S.A.L.M., 1981. Parametric analyses of mortality rates in bioassays. Water Res. 15, 107–119.

Kooijman, S.A.L.M., 2000. Dynamic Energy and Mass Budgets in Biological Systems. Cambridge University Press, Cambridge.

McCarty, L.S., Mackay, D., 1993. Enhancing ecotoxicological modeling and assessment, body residues and modes of toxic action. Environ. Sci. Technol. 27, 1719–1728.

Schwarzenbach, R.P., Gschwend, P.M., Imboden, D.M., 1993. Environmental Organic Chemistry. John Wiley & Sons, New York.

Sijm, D.T.H.M., Van der Linde, A., 1995. Size-dependent bioconcentration kinetics of hydrophobic organic chemicals in fish based on diffusive mass transfer and allometric relationships. Environ. Sci. Technol. 29, 2769–2777.

Thomann, R.V., 1989. Bioaccumulation model of organic chemical distribution in aquatic food chains. Environ. Sci. Technol. 23, 677–707.

Vaes, W.H.J., Hamwijk, C., Urrestarazu Ramos, E., Verhaar, H.J.M., Hermens, J.L.M., 1996. Partitioning of organic chemicals to polyacrylate-coated solid phase microextraction (spme) fibers: kinetic behavior and quantitative structure–property relationships. Anal. Chem. 68, 4458–4462.

Verbruggen, E.M.J., Vaes, W.H.J., Parkerton, T.F., Hermens, J.L.M., 2000. Polyacrylate-coated spme fibers as a tool to simulate body residues and target concentrations of complex organic mixtures for estimation of baseline toxicity. Environ. Sci. Technol. 34, 324–331.