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I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

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"Animal Energy Budgets Affect the Kinetics of Xenobiotics"

S.A.L.M. KOOIJMAN
Free University
Faculty of Biology
1007 MC Amsterdam
The Netherlands

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ANIMAL ENERGY BUDGETS AFFECT THE KINETICS OF XENOBIOTICS

S.A.L.M.Kooijman & R.J.F.van Haren
Free University, Faculty of Biology
P.O.Box 7161, 1007 MC Amsterdam

ABSTRACT

On the basis of a model for energy budgets, which includes the dynamics of stored energy, a model has been proposed for the kinetics of non-metabolized xenobiotic compounds, which may be lipophilic. The surface area coupled uptake is via food and/or water through the aqueous fraction of the animal. The partitioning to non-aqueous structural body mass and to stored materials (i.e. lipids, carbohydrates and proteins) is taken instantaneously. The result is a simple first order kinetics with variable coefficients. The bioconcentration factor has been evaluated. Model predictions have been tested against data from the literature.

INTRODUCTION

The kinetics of xenobiotics is of importance in connection with environmental monitor programs, as preamble for understanding effects of toxic compounds and, as a special case, for medical purposes when the xenobiotic concerns a pharmaceutic. One compartment models do not always give a satisfactory fit with experimental data. For this reason more compartment models has been proposed (see e.g. Curtis *at al* (1977), Ružić (1972)). Because of their larger number of parameters, the fit is better, but an acceptable physical identification of the compartments is usually not possible. These models therefore contribute little to our understanding of the kinetics as a process. The purpose of this paper is to incorporate elementary knowledge about chemical exchange that is not compound-specific and about animal physiology that is not species-specific into a model for the kinetics of non-metabolised compounds.

For terrestrial animals, the usual uptake of xenobiotics from the environment is via food. Sometimes, uptake is via the lung or directly through the surface. In the aquatic environment uptake directly from water is especially

important for hydrophilic organic compounds (Bruggeman *et al.*, 1981) and metals (Borchardt, 1981, Riisgard *et al.*, 1987). In aquatic animals that are chemically isolated from their environment, like aquatic insects, birds and mammals, the usual uptake is through food only. See e.g. Walker (1990) for a discussion of uptake routes. Excretion is through the surface directly, via excretion products and via gametes. Accumulation of lipophilic compounds and partitioning between different organs can be explained by the occurrence of stored lipids. Schneider (1982) found large differences of PCB concentrations in different organs of the cod, but they did not differ when based on the phospholipid-free fraction of extractable lipids. Models for the feeding conditions dependent kinetics have been proposed by e.g. Lassiter & Hallam(1988), Hallam & de Luna(1984), Hallam *et al.*(1989). The models presented in these papers have a large number of parameters. The present paper aims at modelling the kinetics of xenobiotics in a parameter sparse way, assuming instantaneous partitioning of the compound in the organism, as proposed by Barber *et al.*(1988). It differs from their model by the coupling to a model for the uptake and allocation of energy, which has been extensively tested, Evers & Kooijman(1989), Kooijman(1986a, b, c, 1988), Zonneveld & Kooijman(1989). One of the key features of this model is that food uptake, and so excretion, is proportional to surface area, resulting in relatively simple kinetics of xenobiotics allowing several uptake and excretion routes. Other features are a cyclic change in lipid rich compounds, due to the reproductive behaviour and predictions for concentration-body size relations.

MODEL SPECIFICATION

The tissue is divided into four compartments: the aqueous fraction of volume V_a, the non-aqueous fraction of the structural component of the body of volume V_w, the non- aqueous fraction of the stored energy reserves available for utilization of volume V_s, and the non-aqueous fraction of the energy reserves set apart with the destination of reproduction of volume V_r. Energy rich compounds like glycogen, proteins and lipids are assumed to be replaced by water when food conditions grow poor. This has been found for mussels by Pieters *et al.*(1979) and for snails by Zonneveld & Kooijman(1989). We assume that the animal remains isomorphic during its development, from which follows that each organ occupies a fixed fraction of the structural body mass. Moreover we assume homeostasis, i.e. the chemical composition of the

non-aqueous fraction of the structural body mass and the energy reserves remain constant. However, we allow for chemical differences between these two compartments. The aqueous body volume is therefore a fixed fraction of the structural component of the body plus the part of the energy reserves that is not filled with energy rich components. So $V_a = (1 - \alpha_w)W + \alpha_e(1 - e)W$ for W denoting the structural body mass, e the energy reserves as a fraction of the maximum energy reserves, α_w the non-aqueous fraction of the body size and α_e the maximum volume of energy reserves as a fraction of body size. The volume occupied by non-aqueous biomass, energy reserves and reproduction reserves are taken to be $V_w = \alpha_w W$, $V_e = \alpha_e eW$ and $V_r = \alpha_e rW$, where r denotes the cumulative energy investment into reproduction since the last reproductive output as a fraction of the maximum energy reserves. At reproduction it is reset to zero. Wet weight, W_w, of an individual is taken to be

$$W_w = d_s(V_a + V_w + V_e + V_r) = d_s(1 + \alpha_e(1 + r))W \tag{1}$$

where d_s is the specific density, which is close to 1 g/cm^3. The redistribution of the xenobiotic over the four compartments is assumed to be fast with respect to the exchange with the environment (see the section on time scales). This assumption is supported by the study of the elimination rate of 4,4'-dichlorobiphenyl (PCB15) in the pond snail *Lymnaea stagnalis* by Wilbrink *et al.*(1989), who found the elimination rates to be equal for different organs. The fact that structural biomass consists of organs differing in partition coefficients for the xenobiotic, is covered naturally through the assumptions of isomorphism and homeostasis together with instantaneous partitioning. We can therefore relate the total number of moles of xenobiotic inside the animal, C_+, to its concentration in the aqueous fraction, c_a, which is assumed to be the only compartment which communicates directly with the environment. We have

$$\begin{aligned} C_+ &= C_a + C_w + C_e + C_r = V_a c_a + V_w c_w + V_e c_e + V_r c_r \\ &= (1 + \alpha_e + \alpha_w(P_{wa} - 1) + \alpha_e e(P_{ea} - 1) + \alpha_e r P_{ea})\, W c_a \\ &= \alpha_e h W c_a \end{aligned} \tag{2}$$

where the C's denote the amount of xenobiotic compound in moles and the c's the concentrations in mol/volume; $P_{wa} = c_w/c_a$ is the partition coefficient of xenobiotic between the non-aqueous structural biomass and the aqueous

phase; $P_{ea} = c_e/c_a$ that of the energy reserves and the aqueous phase. The partition coefficients are assumed to be fixed values. $\gamma = 1 + \alpha_e^{-1} + (P_{wa} - 1)\alpha_w/\alpha_e$ and

$$h = \gamma + (P_{ea} - 1)e + P_{ea}r \tag{3}$$

are introduced to shorten the notation. See table 1 for a list of the parameters and main variables.

The uptake as well as elimination are assumed to be proportional to the surface area of the isomorphic animal, thus proportional to $W^{2/3}$. See e.g. Evers & Kooijman (1989) for a discussion on the proportionality of ingestion with surface area. Uptake via water is proportional to surface area, because isomorphism ties surface area of e.g. gills to total surface area. We assume that water is locally well mixed, such that the animal will not deplete its immediate surroundings from xenobiotic. So we do not follow e.g. Norstrom *et al.*(1976) by relating uptake to oxygen consumption. The absence of the connection between oxygen uptake and accumulation of PCB in guppies has been experimentally supported by Opperhuizen & Schrap (1987). When a simple diffusion type of kinetics applies, we arrive at

$$C'_+ = W^{2/3}\left(r^*_{da}c_d + r^*_{pa}fc_p - r^*_{ad}c_a\right) \tag{4}$$

where the r^*'s denote the transport rates from the compartment indicated in the first index to the second one and f denotes the scaled functional response $f = X/(K+X)$, for K being the saturation constant and X the food density. From (2) we obtain

$$C'_+ = \alpha_e(hW)c'_a + \alpha_e(h'W + hW')c_a \tag{5}$$

Substitution into (4) results in

$$c'_a = \frac{r_{da}c_d + r_{pa}fc_p}{hW^{1/3}} - c_a\left(\frac{r_{ad}}{hW^{1/3}} + \frac{W'}{W} + \frac{h'}{h}\right) \tag{6}$$

where $r_{da} = r^*_{da}/\alpha_e$, $r_{pa} = r^*_{pa}/\alpha_e$ and $r_{ad} = r^*_{ad}/\alpha_e$. Although this equation defines, together with an initial condition, the dynamics of the xenobiotic in the animal, it will be difficult, if not impossible to measure the concentration in the aqueous fraction. More relevant seems the concentration in the wet weight $c_{ww} = C_+/W_w$. Substitution of (1) and (2) gives

Table 1: The parameters and main variables of the xenobiotic and the energy budget model.

Par.	Var.	Dimension	Interpretation
	c_d	mol.length^{-3}	conc. in the water
	c_p	mol.length^{-3}	conc. in the food (as volume)
	c_{ww}	mol.weight^{-1}	conc. on the basis of wet weight
r_{pa}		length.time^{-1}	uptake rate from food
r_{da}		length.time^{-1}	uptake rate from water
r_{ad}		length.time^{-1}	elimination rate
P_{ea}		-	partition coeff. en.reserves/aqueous fraction
γ		-	compound parameter
	f	-	food density/saturation const. plus food density
	W	length^3	body size
	e	-	energy reserves/max.energy reserves
	r	-	cum.energy to reprod./max.energy reserves
α_e		-	max.vol.reserves/vol.body
d_s		weight.length^{-3}	specific density of the body
v		length.time^{-1}	energy conductance
κ		-	fraction utilized energy to growth + maint.
a		-	costs of growth/κ max.energy density
b		time^{-1}	maintenance costs/κ max.energy density
W_b		length^3	body size at hatching
W_j		length^3	body size at first maturation
t_s		time	time at spawning or reproduction, $s = 1, 2, ..$

$$c_{ww} = \frac{c_a h}{d_s(1 + \alpha_e^{-1} + r)} \tag{7}$$

After substitution into (6) and application of the chain rule for differentiation again, we arrive at

$$c'_{ww} = \frac{r_{da}c_d + r_{pa}f c_p}{d_s(1 + \alpha_e^{-1} + r)W^{1/3}} - c_{ww}\left(\frac{r_{ad}}{hW^{1/3}} + \frac{W'}{W} + \frac{r'}{1 + \alpha_e^{-1} + r}\right) \tag{8}$$

This description of the kinetics of a xenobiotic has thus 6 free parameters: r_{da}, r_{pa} and r_{ad} of dimension length per time and the dimensionless parameters α_e, γ and P_{ea}. See table 1 for a list of primary parameters and variables.

To complete the model, it is necessary to specify the processes of feeding, storage, growth and reproduction. Following Kooijman(1986), food intake is taken to be a hyperbolic function of food density and proportional to surface area. Assimilation energy stocks the energy storage. Expressed as a density, so a ratio of stored energy and body volume, energy storage follows a simple first order dynamics, with a rate inversely proportional to body length. A fixed fraction of the energy utilized from storage, is spent on growth plus maintenance. The latter is taken proportional to body volume. The rest of the utilized energy is spent on development plus reproduction. The latter drain is first collected in a buffer, which is emptied at spawnings, triggered by environmental factors. Development stops and reproduction starts as soon as a certain cumulated amount of energy is spent on increasing the state of maturity, which here occurs upon reaching a certain body size. The energetic costs of maintaining a certain degree of maturation is taken proportional to the minimum of the actual body volume and that at first maturation, at the expense of the energy flow to development and reproduction (see Zonneveld & Kooijman, 1989). Here, we will express the stored energy density and energy allocated to reproduction as fractions of the maximum stored energy density, which thus become dimensionless quantities. These model elements result in the following dynamics for body volume, scaled energy density and scaled energy allocation to reproduction:

$$W' = \frac{(evW^{2/3} - bW)_+}{e + a} \tag{9}$$

$$e' = vW^{-1/3}(f - e) \tag{10}$$

$$R' = \frac{(1 - \kappa)e}{e + a}(vaW^{2/3} + bW) - (1 - \kappa)bW_j \tag{11}$$

$$R' = \begin{cases} evW^{2/3} - \kappa bW - (1-\kappa)bW_j & \text{for } e \geq W^{1/3}b/v \text{ and } W > W_j \\ evW^{2/3} - \kappa bW & \text{for } e < W^{1/3}b/v \text{ and } W > W_j \end{cases} \quad (12)$$

Now, $r = R/W$ and $R = \int_{t_r}^{t} R'dt$, where t_r denotes the time of latest reproduction, which should not be earlier than the time at first maturation, i.e. when $W = W_j$. The change in reproduction energy density, r', is found through its definition $r' = R'/W - RW'/W^2$

For spawning occurring at t_s, we still have to define the behaviour of c_{ww} around this time point. Kooijman(1986c) argued that a freshly laid egg can be realistically regarded as material representing an amount of stored energy, with a negligible size of structural biomass. Little chemical transformation is required to transform energy set apart for reproduction into that of eggs. Therefore it seems straightforward, at least for females, to let transduce the xenobiotic that rests in these reserves to eggs. We can relate the concentration in the wet weight just after spawning, i.e. at t_s^+, to that just before spawning, i.e. at t_s^-, arriving at

$$c_{ww}(t_s^+) = c_{ww}(t_s^-)\frac{1+\alpha_e^{-1}+r}{1+\alpha_e^{-1}}\frac{h(t_s^+)}{h(t_s^-)} \quad (13)$$

For $P_{ea} < 1 + (P_{wa} - 1)\alpha_w/(1 + \alpha_e(1-e))$ this means a decrease in c_{ww}. So, for a well fed animal for which $e = 1$, $P_{ea} < 1 + (P_{wa} - 1)\alpha_w$ means a decrease in c_{ww} at spawning. Independent from a change in c_{ww} at t_s, the production of eggs makes up an elimination route which can be substantial.

When reproduction occurs as soon as enough energy has been accumulated for a single egg and the energy investment in an egg is small, thus r is negligibly small, we can not simply put $r = 0$ in (8), despite the fact that according to (13) c_{ww} does not change at t_s. The reason is that the time between subsequent spawnings can in this case reduce as well. This means that the elimination rate of size $P_{ea}\alpha_e R' c_a$, which should then be introduced into (4), need not be negligibly small. As a consequence, h'/h in the second term of (6) and $\frac{r'}{r+1+\alpha^{-1}}$ in the second term of (8) should be replaced by $P_{ea}r'/h$. After these substitutions, we can safely put $r = 0$ and still obeying the preservation law for the xenobiotic. Species differ widely in the timing of the reproduction process. Small animals, like those in plankton usually reproduce more or less continuously, while the larger ones in temperate climates usually reproduce once a year only.

It is also possibile is that no xenobiotic is transduced through the reproduction process, as has been found by Wilbrink *et al.*(1989) for 4,4'-DCB in *Lymnaea*. In that case the last factor in (13) should be omitted, resulting in an increase of c_{ww} due to the reduction in wet weight.

Figures 1 & 2 illustrate the performance of the model to describe the accumulation / elimination behaviour of the compounds hexachlorobenzene ($\log K_{ow}$ = 5.45, Russel & Gobas, 1989) and 2- monochloronaphthalene ($\log K_{ow}$ = 3.90, Opperhuizen, 1986). The mussel and fish, respectively, were not fed during the experiment, which implies that their energy reserves decreased during the experiment. As a consequence the small fish kept at a bit higher temperature than the larger mussel, depleted its energy reserves relatively faster, so that it starts to eliminate during the accumulation phase of the experiment. (See Kooijman, 1986b for a theory on the relation between body size and energy reserves.) The model succesfully describes this phenomenon. The experiments have been short enough to assume that the size of the test animals did not change and that the energy allocation to reproduction has been negligibly small during the experiment. The concentration in water changed during accumulation. We therefore fitted a cubic spline to these concentrations and used this spline in (8) to obtain the concentrations in the wet weight. The free parameters have been estimated according to the least squares criterion.

INITIAL CONDITIONS

Although the concentration in the hatchling contributes little to that later on because of the factor $W^{-1/3}$ in (8), consistency requires its evaluation. If the xenobiotic is transferred from mother to hatchling, the initial value of c_{ww} depends on the contents of xenobiotic in the mother and her feeding condition. Experience with chronic toxicity tests learns that most effects occur at hatching, meaning that an egg must be considered as chemically rather isolated from its environment, apart from gas exchange of course. Neglecting the contribution via sperm, the c_{ww} of the hatchling therefore equals the ratio of content of xenobiotic of the egg at formation in the mother and its wet weight $d_s(1+\alpha_e)W_b$. The energy content of an egg as a fraction of maximum energy reserve of the hatchling is according to Kooijman(1986c)

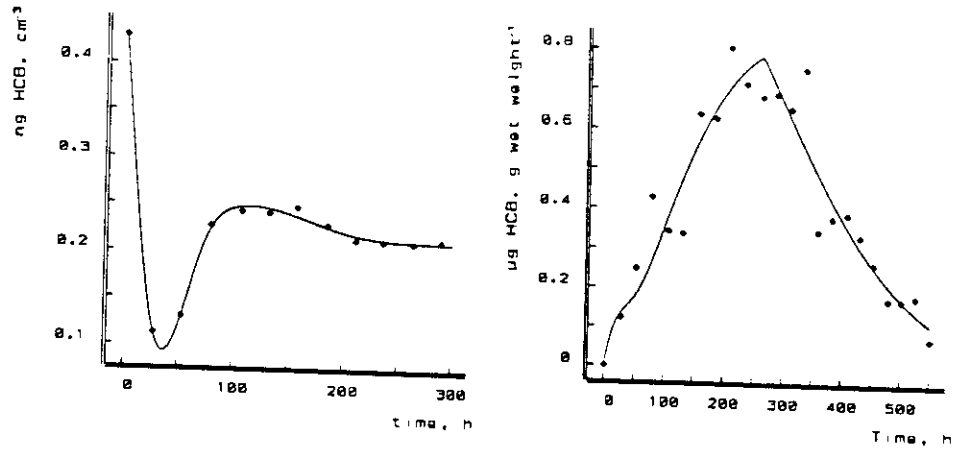


Figure 1: The measured concentration of hexachlorobenzene in the water and in the 6.03 cm^3 freshwater mussel *Elliptio complanata* at 20°C during an 264 h accumulation / elimination experiment. Data from Russel & Gobas (1989). The least squares fitted curves are the cubic spline function for concentrations in the water and the model based expectation for that in the wet weight. The parameter values with s.d. were $r_{da}/(1 + \alpha_e^{-1} + r) = 36.5$ (3.7) $cm.h^{-1}$, $e(0)P_{ea}/\delta = 10.5$ (16.12), $r_{ad}/\delta v = 2.63$ (2.56) for $v = 0.01$ $cm.h^{-1}$ with $\delta = \gamma + P_{ea}r$.

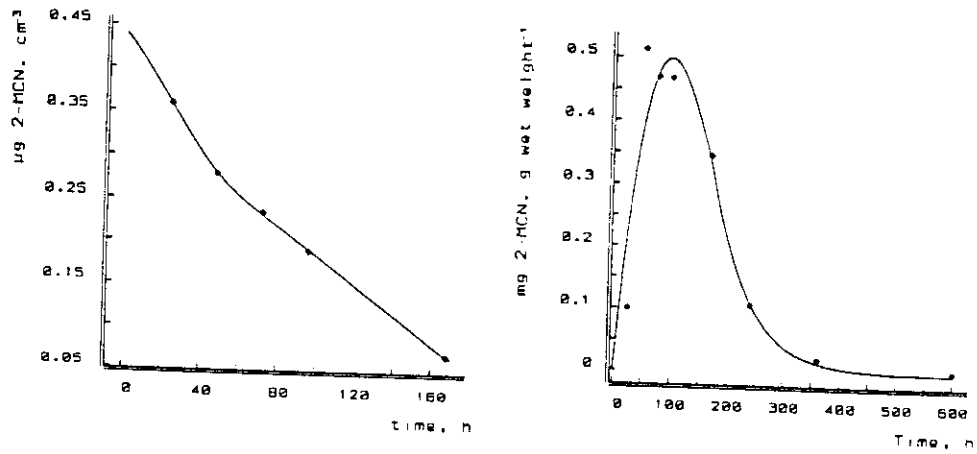


Figure 2: The measured concentration of 2-monochloronaphthalene in the water and in the 0.22 cm^3 female guppy *Poecilia reticulata* at 22°C during an 168 h accumulation / elimination experiment. Data from Opperhuizen (1986). The least squares fitted curves are the cubic spline function for the concentrations in the water and the model based expectation for that in the wet weight. The parameter values with s.d. were $r_{da}/(1 + \alpha_e^{-1} + r) = 15.3$ (3.4) $cm.h^{-1}$, $e(0)P_{ea}/\delta = 6.0$ (12), $r_{ad}/\delta v = 0.72$ (0.30) for $v = 0.014$ $cm.h^{-1}$ with $\delta = \gamma + P_{ea}r$.

$$e_0 = 1.1a + e_b\left(1 - \frac{1}{4e_b}\left(\frac{W_b}{W_m}\right)^{1/3}\right)^{-3} \tag{14}$$

where the scaled reserve energy density of the hatchling, e_b, equals that of the mother at egg formation and the maximum body size $W_m = (v/b)^3$. The initial content in the egg is in accordance with (2): $c_a\alpha_e P_{ea} e_0 W_b$, where c_a is the concentration in the aqueous phase of the mother at egg formation. Substitution of (7) results in

$$c_{ww}(0) = c_{ww}\frac{P_{ea}e_0(1 + r/(1+\alpha_e^{-1}))}{\gamma + (P_{ea}-1)e + P_{ea}r} \tag{15}$$

where c_{ww}, e and r refer to the values of the mother at the moment of egg formation.

TIME SCALES

From (8), we observe that the relaxation time of c_{ww} equals

$$\left(\frac{r_{ad}}{hW^{1/3}} + \frac{W'}{W} + \frac{r'}{1+\alpha_e^{-1}+r}\right)^{-1}$$

Its maximum value is obtained for $W' = 0$, $r' = 0$, $W = W_m$, $e = 1$ just before spawning, where $r = r_m = \int_0^{t_i} r'dt$. The maximum relaxation time is then $W_m^{1/3}(\gamma - 1 + P_{ea}(1+r_m))r_{ad}^{-1}$. Its minimum value is obtained for $W = W_b$, which implies, $r' = r = 0$. The relaxation time reduces to $\frac{l_b}{b}(\frac{\alpha}{1+\beta e} + \frac{e-l_b}{e+a})$, for $l_b = W_b^{1/3}b/v$, $\alpha = \frac{r_{ad}}{v\gamma}$ and $\beta = \frac{P_{ea}-1}{\gamma}$. Its minimum value is obtained for

$$e = \min\{1, \max\{l_b, \frac{l_b + a - \alpha a \pm (1-\beta a)\sqrt{(l_b+a)\alpha/\beta}}{\alpha - \beta(l_b+a)}\}\}$$

For increasing lipophilicity, so P_{ea} and thus β increase, the relaxation time increases. The minimum value tends to $\frac{l_b}{b}\frac{1+a}{1-l_b}$, which completely depends on the energy budget. This minimum relaxation time sets the time frame for the present model. All processes with much smaller relaxation times, like the kinetics of the xenobiotic and storage materials in the blood compartment (c.f. Bruggeman *et al.*(1981)) can be regarded as being in pseudo equilibrium. So, the assumption of instantaneous partitioning of the xenobiotic compound

can be relaxed to the condition that the relaxation time of the redistribution process is small in comparison with this minimal value.

When the rate $r_{ad}/hW^{1/3}$ is large with respect to $W'/W + r'/(1+\alpha^{-1}+r)$, the model reduces to a simple first order kinetics, but the parameters still depend on the size of the organism.

BIOCONCENTRATION FACTOR

The bioconcentration factor, BF, is an important concept in the kinetics of xenobiotics. It is usually defined as the ratio of the concentration in the organism and the concentration in the environment, which both are taken constant. This implies that food density is taken constant as well. In the strict sense, the present model does not have such a factor, because the energy set apart for reproduction shows a cyclic behaviour, so does the BF. We can approach the concept BF for animals that ceased growth, so $W' = 0$. At constant food density this occurs when they reach their ultimate size $W_\infty = (fv/b)^3$. The energy density then becomes $e = f$. The energy density set apart for reproduction is $r = tr'$, where t represents the time since last spawning. For this particular values for W and e we have from (11) $r' = (1-\kappa)b(1 - W_j/W_\infty)_+$. Therefore we have

$$h(t) = \gamma + (P_{ea} - 1)f + P_{ea}r't$$

which is linear in t. This simplifies (8) to an extent that it can be solved explicitly, giving

$$\begin{aligned}
c_{ww}(t) &= v(t)\left(\int_0^t \frac{u(x)}{v(x)}dx + c_{ww}(0)\right) \text{ where} \\
u(x) &= W_\infty^{-1/3}\frac{r_{da}c_d + r_{pa}fc_p}{d_s(1+\alpha_e^{-1}+xr')} \text{ and} \\
v(x) &= \exp\{-\int_0^x \left(\frac{r_{ad}}{h(y)W_\infty^{1/3}} + \frac{r'}{1+\alpha_e^{-1}+r'y}\right)dy\} \\
&= \frac{1+\alpha_e^{-1}}{1+\alpha_e^{-1}+xr'}\left(\frac{h(0)}{h(x)}\right)^{r_{ad}/W_\infty^{1/3}r'P_{ea}}
\end{aligned}$$

When t_i is the period between subsequent broods or spawnings and t_s is time at spawning, in equilibrium we must have that $c_{ww}(t_s^+ + t_i) = c_{ww}(t_s^-)$. Using

(13), which we rewrite as $c_{ww}(t_s^-) = c_{ww}(t_s^+)g(t_i)$ with $r = tr'$, we can solve $c_{ww}(t_s^+)$ and obtain

$$\begin{aligned} c_{ww}(t_s^+) &= \frac{\int_0^{t_i} u(x)/v(x)\,dx}{g(t_i)/v(t_i) - 1} \\ &= \frac{r_{da}c_d + r_{pa}fc_p}{d_s(1+\alpha_e^{-1})} \frac{\gamma + f(P_{ea}-1)}{r_{ad} + W_\infty^{1/3}P_{ea}r'} \end{aligned} \tag{16}$$

In order to arrive at the BF, we have to divide by the concentration in the environment. Sometimes, the water concentration is taken for aquatic organisms, but it seems more lucid to include the xenobiotic in the food in the environment as well. In that case, the BF just after spawning is given by $c_{ww}(t_s^+)(c_d + Xc_p)^{-1}$, while that just before spawning is $g(t_i)$ times as large. In any case, the BF still depends on the concentration in the environment as long as uptake via food contributes significantly. This greatly reduces the usefulness of this concept.

CONSTANT ENVIRONMENTS

When food density, as well as the concentration of xenobiotic in the water and in the food do not change since long, the concentration in the food will be proportional to that in the water, let us say $c_p = P_{pd}c_d$. The energy density will be constant at $e = f$. When we choose the maximum length, $W_m^{1/3} = v/b$ as our unit for length l, b^{-1} as unit for time t°, and c_d as unit for concentration in the wet weight c, we effectively remove all dimensions of the problem and obtain a maximum reduction of the number of parameters. Scaled length as function of scaled age is found from (9):

$$l(t^\circ) = f - (f - l_b)\exp\{\frac{-t^\circ}{3(f+a)}\} \tag{17}$$

The energy drain to reproduction rate as a fraction of the maximum stored energy reduces for small amounts of accumulated energy for reproduction to

$$r'(t^\circ) = (1-\kappa)\left(\frac{f + af/l(t^\circ)}{f+a} - \frac{l_j^3}{l^3(t^\circ)}\right) \tag{18}$$

The dynamics of the scaled concentration in the wet weight now reduces for $l < l_j$ from (8) to

$$c'(t^\circ) = \frac{r^\circ_{da} + f r^\circ_{pa}}{l(t^\circ)} - c(t^\circ)\left(\frac{r^\circ_{ad}/l(t^\circ)}{\gamma + (P_{ea}-1)f} + \frac{f/l(t^\circ) - 1}{a+f}\right) \tag{19}$$

where the new dimensionless compound parameters are $r^\circ_{da} = \frac{r_{da}}{bW_m^{1/3}} \frac{1}{d_s(1+\alpha_e^{-1})}$, $r^\circ_{pa} = \frac{r_{pa}}{bW_m^{1/3}} \frac{P_{pd}}{d_s(1+\alpha_e^{-1})}$ and $r^\circ_{ad} = \frac{r_{ad}}{bW_m^{1/3}}$. For $l > l_j$, thus after an scaled age of $3(a+f)\ln\frac{f-l_b}{f-l_j}$, the dynamics depends on the times of spawning. For short periods between subsequent broods and small amounts of energy accumulated for reproduction we have:

$$c'(t^\circ) = \frac{r^\circ_{da} + f r^\circ_{pa}}{l(t^\circ)} - c(t^\circ)\left(\frac{r^\circ_{ad}/l(t^\circ) + P_{ea} r'(t^\circ)}{\gamma + (P_{ea}-1)f} + \frac{f/l(t^\circ) - 1}{a+f}\right) \tag{20}$$

The initial scaled concentration depends on the size of the mother. When we consider a young born from a fully grown mother, which thus has a scaled length of $l = f$, a scaled energy drain to reproduction of $r' = (1-\kappa)(1-l_j^3/f^3)$, and a concentration of

$$c(\infty) = \frac{(\gamma + f(P_{ea}-1))(r^\circ_{da} + f r^\circ_{pa})}{r^\circ_{ad} + f P_{ea}(1-\kappa)(1-l_j^3/f^3)} \tag{21}$$

The scaled initial concentration becomes from(15):

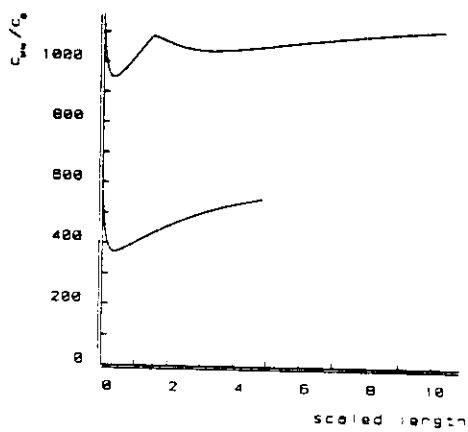
$$c(0) = \frac{e_0 P_{ea}(r^\circ_{da} + f r^\circ_{pa})}{r^\circ_{ad} + f P_{ea}(1-\kappa)(1-l_j^3/f^3)} \tag{22}$$

The concentration in the wet weight will increase during the lifetime of an individual when

$$\frac{c(\infty)}{c(0)} = \frac{\gamma + f(P_{ea}-1)}{e_0 P_{ea}} > 1 \tag{23}$$

Depending on the exchange rates relative to the growth rate, the concentration will first drop after hatching because of the dilution through growth. At maturation, the acculumation in females can decrease due to elimination through reproduction. As an example, c is given as a function of t° Fig.3. An important conclusion from this figure is that the fact that a xenobiotic slowly accumulates into an animal not only depends on the proporties of the xenobiotic, but also on the changing physiology of the animal.

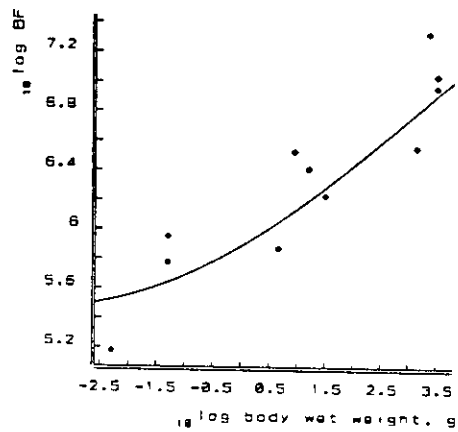
Figure 3: The concentration of xenobiotic on the basis of wet weight as a fraction of that in the water, as a function of scaled age in a constant environment. The xenobiotic parameters are $r^\circ_{da} = 20$, $r^\circ_{pa} = 1000$, $r^\circ_{ad} = 50$, $\gamma = 30$ and $P_{ea} = 100$. The energetic parameters are $l_b = 0.1$, $l_j = 0.4$, $a = 0.2$, $\kappa = 0.3$ for $f = 1$ (upper curve) and $f = 0.4$ (lower curve).



BODY SIZE RELATIONS

Since energy budgets depend on body size, we can expect that the BF based on (16) as well depends on the ultimate body size a species can reach. The theory behind this reasoning is presented in Kooijman (1986b). For studying the BF-body size relation, we assume that reproduction takes place once a year for all species. Since r_{pa} is proportional to the surface area-specific ingestion rate, the theory states that it is proportional to the cubic root of the body size. This also holds for the maximum storage density (Kooijman, 1988), thus for b^{-1}, which makes $W_\infty^{1/3} r'$ independent from body size. Although the maximum storage density scales with the cubic root of body size, it does not imply that the volume of the reserves as a fraction of that of the body scales in this way. Large animals seem to utilize storage compounds with a higher energy capacity more frequently. Nonetheless, α_e will increase, thus γ will decrease with body size, but we expect that this is of minor influence on the BF. The other parameters, r_{da}, r_{ad}, P_{ea}, P_{wa}, α_w, κ, W_j/W_∞, d_s do not depend on body size. Therefore we expect that the BF at high food densities is linear in the cubic root of body size, with a slope depending on the uptake via food, em i.e. $BF \propto r_{da} + r_{pa} P_{pd}$. Note that we did not assume any interference of uptake and elimination (or transformation) with the metabolism of the animal. Figure 4 illustrates that the BF for the highly lipophyllic compound 2,4,5,2',4',5' hexachlorobiphenyl (PCB153) for aquatic animals depends on body size indeed, and that this can be explained on the basis of the present reasoning.

Figure 4: The bioconcentration factor for PCB153 in aquatic organisms in the field, as given in Oliver & Niimi(1988), Niimi & Oliver (1989) and from the Dutch Ministry of Public Works and Transport. The curve represents the least squares fit of the linear relationship between the BF and the cubic root of the body size. $\frac{r_{da}}{r_{pa}P_{pd}}(\frac{d_s}{W_w})^{1/3} = 2.18$ cm^{-1}.



DISCUSSION

The results presented in this paper support the already widely accepted view that the kinetics of at least some compounds depend on the lipid content, thus on the feeding condition of the animal. The understandig of the kinetics therefore requires a notion of the energy uptake, use and allocation by the animal. With a well tested and relatively simple model for the latter at hand, we are able to cope with a rich variety of kinetics on the basis of very simple uptake and elimination behaviour of the compound. It does not seem feasible to use data on the kinetics of xenobiotics to obtain parameter values related to the energy budget of the animals under the test conditions. This should be done more directly. Since little attention hase been given in the literature to the physiology of the experimental animals, this model for the kinetics, as well as competing ones, can not be tested rigorously at the moment. The large standard deviations of the parameter estimates is a result of this problem. We think that the present exercise does make clear that it is really hard to test models assuming complex uptake mechanisms as long as obvious physiological changes related to the nutrition are not considered.

The usual effect of metabolism on xenobiotic organic compounds is a reduction of the lipophilicity. It is not difficult to incorporate e.g. Michaelis-Menten kinetics for this transformation. The result will be a decrease in the overall level. The logic behind this mechanism can be seen when toxic effects occur upon accumulation beyond some threshold value. Some LC50-time curves could well be described this way (Kooijman, 1981, 1983). Because

of the instantaneous partitioning, crossing a threshold value in the aqueous phase corresponds with crossing some other threshold value in another phase. It therefore does not matter where we place the threshold, as long as it is a free parameter, to be estimated from observed effects. This is obviously a pleasant property of a model that is not compound specific. When the metabolites are more toxic than the original compound and reach significant levels, the whole process is of course much more complex.

In Kooijman & Metz(1983), a toxic compound is assumed to affect parameter values of the energy budget model. Although this implies a highly time varying effect for dynamical populations, it is basically a static approach. The present formulation allows a dynamical approach. Since the concentration of a wide class of chemicals is predicted to increase with size, so usually with age, the model offers one possible explanation for lifetime reducing effects of chemicals.

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