Scaling relationships based on partition coefficients and body sizes have similarities and interactions

published in
SAR and QSAR in Environmental Research
2007

DOI (link to publisher)
10.1080/10629360701304196

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Download date: 15. Apr. 2022
Scaling relationships based on partition coefficients and body sizes have similarities and interactions

S. A. L. M. Kooijman; J. Baas; D. Bontje; M. Broerse; T. Jager; C. A. M. Van Gestel; B. Van Hattum

Faculty Earth & Life Sciences, Vrije Universiteit, 1081 HV Amsterdam, The Netherlands

Online publication date: 04 December 2010

To cite this Article Kooijman, S. A. L. M., Baas, J., Bontje, D., Broerse, M., Jager, T., Van Gestel, C. A. M. and Van Hattum, B.(2007) 'Scaling relationships based on partition coefficients and body sizes have similarities and interactions', SAR and QSAR in Environmental Research, 18: 3, 315 — 330

To link to this Article DOI: 10.1080/10629360701304196
URL: http://dx.doi.org/10.1080/10629360701304196

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
Scaling relationships based on partition coefficients and body sizes have similarities and interactions


Faculty Earth & Life Sciences, Vrije Universiteit, de Boelelaan 1085, 1081 HV Amsterdam, The Netherlands

(Received 24 April 2006; in final form 6 October 2006)

The LC₅₀ of compounds with a similar biological effect, at a given exposure period, is frequently plotted log–log against the octanol–water partition coefficient and a straight line is fitted for interpolation purposes. This is also frequently done for physiological properties, such as the weight-specific respiration rate, as function of the body weight of individuals. This paper focuses on the remarkable observation that theoretical explanations for these relationships also have strong similarities. Both can be understood as result of the covariation of the values of parameters of models of a particular type for the underlying processes, while this covariation follows logically from the model structure. The one-compartment model for the uptake and elimination of compounds by organisms is basic to the BioConcentration Factor (BCF), or the partition coefficient; the standard Dynamic Energy Budget model is basic to the (ultimate) body size. The BCF is the ratio of the uptake and the elimination rates; the maximum body length is the ratio of the assimilation (i.e. uptake of resources) and the maintenance (i.e. use of resources) rates. This paper discusses some shortcomings of descriptive approaches and conceptual aspects of theoretical explanations. The strength of the theory is in the combination of why metabolic transformation depends both on the BCF and the body size. We illustrate the application of the theory with several data sets from the literature.

Keywords: Scaling relationships; Toxico-kinetics; Effects; Body size; Modified compartment models; Bioconcentration factor; Film models; Dynamic Energy Budget theory

1. Introduction

An effect of a chemical compound on an organism is defined as a compound-induced change in its physiology, compared to the unstressed situation. Effects depend on the properties of the chemical compound, of the organism and on the concentration of the compound. All chemical compounds have three concentration ranges: ‘too little’, ‘enough’ and ‘too much’. Some of these ranges might be zero for some compounds.

*Corresponding author. Email: bas@bio.vu.nl
†Presented at the 12th International Workshop on Quantitative Structure–Activity Relationships in Environment Toxicology (QSAR2006), 8–12 May 2006, Lyon, France.
If the concentration is in the ‘enough’ range, the compound is said to have no effect, so concentration-related effects imply a comparison of physiological behaviour with that in concentrations within the ‘enough’ range. We here focus on the ‘too much’ range, with special interest for the lower boundary of this range, where the compound induces small effects.

Two very different categories of properties of chemicals are of importance to understand their effects on biota: properties that relate to the number of molecules in an organism (to transport) and to the effects per molecule (to activity). General theory for the latter category is presently not well understood; this paper is about theory for the first category. Theory that links these molecular properties of chemical compounds to their effects on organisms benefit from a closer look at such effects in general. Effects of chemicals on the performance of organisms can best be understood by relating the effects to internal concentrations [1] and linking the concentrations to changes in the parameters of a model for the performance of organisms relative to the unstressed situation. This makes the molecular properties that relate to toxicokinetics also relate to effects. If effects are just linked to external concentrations it will be difficult to distinguish between a small number of highly active molecules or a large number of poorly active molecules; it is important to distinguish between these two cases if different chemicals are compared. As long as the effects are small the changes in parameter values can be taken linear [2, 3]. This means that we need two types of models to specify effects of toxicants on biota: a toxicokinetic model and a model for the physiological performance of organisms. We focus here on partition coefficients as a molecular property in more detail, neglecting properties that relate to the transport rates (e.g. across living membranes).

The most simple model for toxicokinetics is the one-compartment model, a term first introduced by Sheppard [4], and is the basis for a wide variety of extensions, such as the multi-compartment models [5, 6] for single organisms or food webs [7, 8], which found their applications in e.g. pharmacology and mixture toxicology [9, 10].

The situation is more complex for the physiological performance of organisms, because many physiological processes, such as assimilation, maintenance, growth, development, reproduction and aging, are tightly interlinked, which complicates the model. Since two decades ago, however, the Dynamic Energy Budget (DEB) theory [11, 12] has been developed for the purpose of specifying how these processes interrelate. It applies to all species of organisms and many popular empirical models for particular aspects turned out to be special cases of the standard DEB model, e.g. Pirt’s model for microbial growth [13], Droop’s model for algal growth [14], von Bertalanffy’s model for animal growth [15], Hugget-Widdas’ model for foetal growth [16], Leudeking-Piret’s model for microbial product formation [17], Holling’s model for feeding [18], Kleiber’s law for respiration [19], Weibull’s model for aging [20].

The standard DEB model considers the individual as a dynamic system with basically two variable states: reserve and structure. Substrate (food, nutrients) is taken from the environment and converted to reserve before use for various metabolic endpoints, such as maintenance, growth and reproduction. The behaviour of the system is specified by a set of differential equations that follow from first principles, i.e. a set of simple assumptions about the chemistry and physics behind the metabolic organisation that makes sense in a wider context than the description of this organisation as such. These equations have parameters that are basically constant and individual-specific. In an early stage of the development of the DEB theory it became obvious that
the parameters tend to covary between species in ways that are predictable by the
theory [21], without using any empirical argument. It is a tendency only, and
evolutionary specialisation and adaptation can cause species-specific deviations from
the expected patterns, but these deviations turn out to be relatively small. We tried
the same line of reasoning on the one-compartment model and also found that for
this model it is possible to arrive at theoretical predictions for the covariation of param-
eter values, without using any empirical argument [22]. This is very remarkable, because
the reasoning behind the variation of parameter values certainly cannot be applied
generally, so the DEB model and the one-compartment model share some basic
properties. The reasoning does not apply, for instance, to the whole class of production
models for bioenergetics [11]. In these popular models, maintenance is directly paid
from assimilation and set-point rules control the allocation to growth versus
reproduction. These set-point rules are typically empirically inspired, which hampers
the derivation of how parameter values covary among species.

The primary purpose of this paper is to reveal the similarities between both
models conceptually to uncover the reason why it is possible to predict the covariation
of parameter values on the basis of first principles. We then discuss some of the
extensions of the models and their interactions to understand the role of metabolic
activity in transformations, effects and toxico-kinetics.

The covariation of parameter values found its application in QSPRS and body size
scaling relationships. Many thousands of references discuss empirical methods that
are based on linear regression of log-log transformed data, see Bradbury et al. [23]
for a recent review for QSPRS and Peters [24] for a useful compilation of data
for body size scaling relationships. This amounts to allometric relationships between
measured quantities and partition coefficients or body weights. Although such
regressions sometimes result in descriptions that are useful for interpolation purposes,
the lack of understanding and the frequently present huge scatter hampers further progress along this line of reasoning (see the discussion section). This is a pity, because
both QSPRS and body size scaling relationships can be very useful in practice.
This motivates our search for theoretical underpinning.

We first discuss the reasoning behind the covariation of parameter values for the
one-compartment model and the standard DEB model.

2. One-compartment model and extensions

The one-compartment model basically specifies that uptake of a chemical compound is
proportional to the external concentration, and elimination proportional to the internal
concentration. The external concentration is typically assumed to be a given function
of time, but if the value depends on the internal concentration the model is called a
1-1 compartment model [22], or a 2-compartment model [10].

In the most simple form, where only aqueous uptake and elimination are considered,
equilibrium between the internal and the external concentration is reached when
the uptake flux equals the elimination flux; the ratio of the internal and external
concentrations is called the BioConcentration Factor $BCF = \frac{b_u}{k_e}$ (mol/Cmol or
mol/kgBW), where $b_u$ is the uptake rate (mol/Cmol·h or mol/kgBW·h), and $k_e$ is the
elimination rate (1/h).
This very simple model has, however, far reaching implications that are not widely recognized. The BCF can be seen as a compound parameter, i.e. a parameter that is a function of other parameters, in this case the uptake and elimination rates. These three parameters (the BCF and the two rates) tend to covary in a way that can be derived from the structure of the model.

By thinking of the organism as a special kind of medium for the chemical compound and of the environment as another medium, we recognize a skew-symmetry in the role of the internal and external concentration; in other words, what we call “internal” and what “external” is arbitrary in an abstract sense. The second observation is that the model rests on fugacity, cf. [8]: the escape rate from a medium is proportional to the concentration in that medium. As explained more formally in Kooijman et al. [22], the combination of these two observations leads to the conclusion that the elimination rate tends to be inversely proportional to the square root of the BCF, and the uptake rate proportional to the square root of the BCF.

The waiting time to acquire a fraction $x$ of the ultimate body burden by a ‘clean’ individual when exposed to a constant concentration of chemical is $t = -k_e^{-1} \ln(1 - x)$, where $k_e$ is the elimination rate. To predict the BCF of different compounds the $n$-octanol–water partition coefficient $P_{ow}$ is frequently used. Octanol is an organic compound that has been selected for its property to mimic lipid phases in tissues and that for neutral hydrophobic compounds the $n$-octanol–water partition coefficient can usually be used as a good predictor for the BCF [7, 25, 26]; since the lipid content of living biomass varies with the nutritional conditions the similarity is limited at best. Moreover, successful algorithms have been developed to compute the $P_{ow}$ from the molecular structure. Hence this waiting time is proportional to $\sqrt{P_{ow}}$, but see the discussion below.

The one-compartment model can be extended into many directions for various purposes. Some extensions include dietary uptake, other elimination or removal routes (such as egestion, dilution by growth, reproductive losses, transformation) and affect the BCF [27]. Some extensions can modify how the rate at which a compartment eliminates depends on the $P_{ow}$. A popular extension in environmental chemistry is the two-film model: two well-mixed media have an interface, and on each side of that interface is a film that is not mixed and where the transport rate is proportional to the concentration gradient of the compound. If formulated in terms of partial differential equations, with the proper boundary condition at the interface, this model is a true extension of the one-compartment model; if the depth of both films reduces to zero, or the diffusive transport rates increase, it reduces smoothly to the one-compartment model. At low diffusive transport rates in the films, the time to loose a certain fraction of the initial load of a body in clean medium is independent of the $P_{ow}$ at low $P_{ow}$ values, and proportional to the $P_{ow}$ at high $P_{ow}$ values. For increasingly higher diffusive transport rates, however, this time is increasingly proportional to the square-root of the $P_{ow}$, because the one-compartment module becomes more and more important. (see figure 1). The technical details are discussed in Kooijman et al. [22].

Some authors assume (incorrectly) that the uptake rate in the one compartment model is proportional to $P_{ow}$, e.g., [28], rather than to $\sqrt{P_{ow}}$. This possibly originates from a wrong treatment of film models, where one-compartment models are used for film models on the assumption that the transport across the bi-film is in steady state.
and the concentration-jump at the interface between the two films equals the partition coefficient \([29, 30]\). This jump in concentration at the interface of the media, however, only equals the partition coefficient, if there is no net transport from one medium to another. See Kooijman et al. \([22]\) for a detailed discussion.

Another type of deviations from the simple square-root relationships between uptake and elimination rates and partition coefficients is caused by ionisation of the compound. As derived in Kooijman \([11]\) these rates at a particular pH value can be written as the square root of a weighted sum of the squared rates at very low and very high pH values. The pH, however, is affected by the compound in a way that depends on its concentration. This leads to interference with the relationships between effects and partition coefficients, because effects occur at particular concentrations that depend on the partition coefficient, and the concentration affects the pH and so the weight coefficients for the rates at very low and very high pH values. In short, we can conclude that the partition coefficient affects the weight coefficients, which modifies toxicity.

Last but not least, large molecules have difficulty in crossing membranes, and molecular weights can have relationships with \(P_{ow}\) values in some groups of compounds. Moreover other properties might also affect transport rates, and might have (complex) relationships with \(P_{ow}\) values.

The step from toxico-kinetics to effects is straightforward on the assumption that each molecule inside the body contributes equally to the effect. If we restrict the comparison of compounds to those with the same effect per molecule, an increase of the BCF (or \(P_{ow}\)) is proportional to the killing rate, and inversely proportional to the No Effect Concentration (NEC) and the tolerance concentrations for the various modes of action \([2, 11, 31]\). The killing rate is the proportionality constant with which the hazard rate (the instantaneous death rate) increases as function of the external concentration, if the toxico-kinetics is in equilibrium. The hazard rate \(h\) at internal
concentration $Q$ amounts to

$$h(Q) = h_0 + B \max(0, Q - Q_0)$$

where the internal killing rate $B$ relates to the external one $b$ as $B = BCF b$. The inverse tolerance concentration is a proportionality constant with which the physiological target parameter (such as the specific maintenance cost) increases with the external concentration, if the toxico-kinetics is in equilibrium. So the parameter value at internal concentration $Q$ equals

$$\text{par}(Q) = \text{par}(0)(1 + Q_0^{-1} \max(0, Q - Q_0))$$

where the internal no-effect concentration $Q_0$ relates to the external no-effect concentration $c_0$ as $Q_0 = BCF c_0$, and the (external) tolerance concentration $c_t$ to the internal one as $Q_t = BCF c_t$. Note that $Q$ will (generally) change in time, even when the external concentration remains constant. Notice also that a small change in the value of the target parameter can result in a large (non-linear) change in the endpoint (growth, reproduction, survival probability); DEB theory specifies how exactly. The label ‘tolerance concentration’ is inspired by the observation that the higher its value, the less toxic the compound. Figure 2 illustrates these predictions, and compares them with data.

As both the tolerance concentration and the hazard rate contain the external concentrations in their dimensions it should be expected that the NEC is inversely proportional to the killing rate. Figure 3 illustrates this relationship for aldehydes, aliphatics and biocides. Notice that the scatter in the data is less than that in figure 2. This is probably because the scatter between the $P_{ow}$ and the BCF does not contribute in this plot, which includes nutrition-induced variations in chemical composition of the body.

### 2.1 Empirical QSPRS

When e.g., $LC_{50}$ values for a certain exposure time are log–log plotted against the octanol–water partition coefficient for a set of compounds with a similar mode of action, a straight line frequently fits the data more or less. In the case of figure 4 a slope of $-0.87$ was found. The value is rather accurate because the scatter is small, thanks to the fact that a single person measured the data accurately using exactly the same experimental setup. The compounds are also similar in their biological effect, so the difference in toxicity is due to differences in the amounts of molecules only. For low $P_{ow}$ values, the elimination rates are high, and the $LC_{50}$ values are close to their asymptotic values. For high $P_{ow}$ values, however, the elimination rates are low and the $LC_{50}$ values can be far away from their asymptotic values (depending on the chosen exposure time). This means that the slope of the line depends on the standardised exposure time. If data are used from different species, the scatter will increase with differences in body size, uptake and elimination kinetics, etc. This means that biological “details” matter, and some of these patterns are predictable if appropriate mechanisms are taken into account.

The scatter in a log–log plot can be expected to be small only when all compounds have the same mode of action (and in fact the same action per molecule inside
Figure 2. The 10 log NEC (left), killing rate (middle) and elimination rate (right) of alkyl benzenes (top) and benzenes, aliphatic compounds and phenols (bottom) as a function of the 10 log octanol/water partition coefficient. The slopes of the lines, i.e. −1, 1 and −0.5, respectively, follow from simple theoretical considerations. The data in the top panels are from the 4d bio-assays on survival of the fathead minnow, as presented in [42]. The partition coefficients were obtained from [43] or calculated according to [44]. The data in the bottom panels are from [45] (NECs, killing rates), [46] (elimination rates). The toxicity data originate from [47–51], as reported in [52].
can make predictions of effects of a particular compound, knowing the effect of a single other one with the same mode of action (and the $P_{ow}$ values of both compounds). Knowing the parameters for compound $j$, that for compound $i$ are given by

$$c_0^i = c_0^j P_{ow}^i / P_{ow}^j, \quad c_l^i = c_l^j P_{ow}^i / P_{ow}^j, \quad b_i = b_l^i P_{ow}^i / P_{ow}^j, \quad k_e^i = k_e^j P_{ow}^i / P_{ow}^j.$$

The step from $(c_0, b, k_e)$ to LC$_x$-time curves can be made with software package DEBtool, which is freely downloadable from http://www.bio.vu.nl/thb/deb/deblab/. This also eliminates the need to define classes of similar compounds; one only has to identify the most similar compound for which toxicity info is available. This still requires a measure for similarity.

Figure 4 also illustrates that 14d-LC$_{50}$ values hardly contain information about how toxicity depends on exposure time, with the consequence that this data set allows some freedom to choose different parameter combinations that describe the data well. This especially concerns the NEC. The LC$_{50}$ hardly reduced after 14 days.
(Könemann pers. comm.), which means that the realistic parameter combination is closer to that of the right panel. This is a strong argument for putting the original data in a database, rather than just summary statistics.

3. Standard DEB model and extensions

The standard DEB model states that food taken up by an individual is converted to reserve; reserve is mobilised for metabolic purposes at a rate that depends on the amounts of reserve and structure. A fixed fraction \( \kappa \) of the mobilised reserve is used for somatic maintenance and growth; the rest is used for maturity maintenance and maturation (in embryos and juveniles) or reproduction (in adults). The maintenance rate is proportional to the amount of structure (in ectotherms), and the food uptake rate is proportional to the surface area of the individual. The parameter values, as listed in Table 1 are individual-specific; they vary somewhat in value among individuals of the same species, and much more between species.

The distinction between a primary and a compound (derived) parameter in the standard DEB model is subtle. Take for instance the trio maximum surface area-specific food ingestion rate \( J_{EAM} \), the maximum surface area-specific reserve assimilation rate \( J_{EAM} \), and the yield of reserve on food \( \gamma_{EX} = J_{EAM} / J_{XAM} \). As long as these three parameters are constant, the choice of which parameter of these three is the compound parameter is arbitrary. However, it is possible to manipulate the environment such that the values of these parameters can change (for instance with temperature or chemical compounds). It then becomes clear which parameters have the most intimate relationships with the underlying processes, but the metabolic organisation has many cross-links so that the identification process is not straightforward. The parameters \( J_{EAM} \) and \( J_{XAM} \) are not both subjected to evolutionary adaptation independently, because basic biochemistry is involved in the conversion \( \gamma_{EX} \), so either \( J_{EAM} \) or \( J_{XAM} \) must be the compound parameter. An increase in the capacity of the digestive system would increase \( J_{XAM} \), but not necessarily \( J_{EAM} \), because this would involve

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Unit</th>
<th>Description</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>( J_{EAM} )</td>
<td>mol d(^{-1})m(^{-2})</td>
<td>Surface area-specific max assimilation rate</td>
<td>Assimilation</td>
</tr>
<tr>
<td>( J_{b} )</td>
<td>m(^{3})m(^{-2})d(^{-1})</td>
<td>Surface area-specific searching rate</td>
<td>Feeding</td>
</tr>
<tr>
<td>( \gamma_{EX} )</td>
<td>mol mol(^{-1})</td>
<td>Yield of reserve on food</td>
<td>Digestion</td>
</tr>
<tr>
<td>( \gamma_{VE} )</td>
<td>mol mol(^{-1})</td>
<td>Yield of structure on reserve</td>
<td>Growth</td>
</tr>
<tr>
<td>( \gamma_{r} )</td>
<td>m d(^{-1})</td>
<td>Energy conductance</td>
<td>Mobilisation</td>
</tr>
<tr>
<td>( J_{ET} )</td>
<td>mol d(^{-1})m(^{-2})</td>
<td>Surface area-specific maint. costs</td>
<td>Heating/osmosis</td>
</tr>
<tr>
<td>( J_{EM} )</td>
<td>mol d(^{-1})m(^{-3})</td>
<td>Volume-specific somatic maintenance</td>
<td>Turnover/activity</td>
</tr>
<tr>
<td>( J_{EJ} )</td>
<td>mol d(^{-1})m(^{-3})</td>
<td>Volume-specific maturity maintenance</td>
<td>Regulation/defence</td>
</tr>
<tr>
<td>( \kappa )</td>
<td>–</td>
<td>Allocation fraction</td>
<td>Allocation</td>
</tr>
<tr>
<td>( \kappa_{R} )</td>
<td>–</td>
<td>Reproduction efficiency</td>
<td>Egg formation</td>
</tr>
<tr>
<td>( E_{J}^{T} )</td>
<td>J m(^{-3})</td>
<td>Maturation at birth</td>
<td>Life history</td>
</tr>
<tr>
<td>( E_{J}^{P} )</td>
<td>J m(^{-3})</td>
<td>Maturation at puberty</td>
<td>Life history</td>
</tr>
<tr>
<td>( h_{a} )</td>
<td>d(^{-2})</td>
<td>Aging acceleration</td>
<td>Aging</td>
</tr>
</tbody>
</table>

Table 1. The primary parameters of the standard DEB model. Only the first one depends on maximum length and is proportional to it.
much more modification of the metabolic capacity. It is, therefore, likely that \( J_{XAm} \) is best choice for being the compound parameter.

Table 1 presents the most natural choice, and, contrary to earlier presentations [11, 21, 32], treats the half saturation constant \( K = (J_{EAm}/J_{EX}(b)) \) and the maximum reserve density \( M_{Em} = (J_{EAm})/v \) as compound parameters and are, therefore, not listed. Stage transitions (from embryo to juvenile and from juvenile to adult) occur if the cumulated investment into maturation exceeds threshold values. It can be shown that this occurs if the amount of structure exceeds a threshold value, if the maturity maintenance costs have a special value. At other values, however, the amount of structure at stage transitions depends on food history. Because size is easier to observe, earlier presentations used length at birth and at puberty as primary parameters but we prefer the more fundamental presentation.

The maximum structural length of an isomorphic individual is given by \( L_m = \kappa (J_{EAm})/J_{EM} \), where \( \kappa \) represents the fraction of mobilized reserve that is allocated to somatic maintenance plus growth, and \( J_{EM} \) the volume-specific somatic maintenance costs. Like the BCF, the maximum length is a ratio of two rates, and like the one-compartment model, the structure of the standard DEB model dictates how the parameters should covary between individuals (especially if they belong to species of very different maximum body sizes) [11, 21]. These references also show that the predictions are in very good agreement with empirical data, for some 35 different eco-physiological quantities. With the choice of primary parameter as presented in table 1 only the surface area-specific reserve assimilation rate depends on maximum size, all others don’t vary with it among species in a systematic way. This parameter must, therefore, be proportional to the maximum length \( L_m \). The next step is to write any quantity of interest, such as the respiration rate, as a function of primary parameters; we know that each primary parameter is either independent of length or proportional to length, so we know how the quantity of interest depends on length.

Table 2 summarises the result for the respiration of subjects that have been starved long enough to ensure that assimilation does not contribute to respiration. Respiration is typically defined as the use of dioxygen, or the production of carbon dioxide or heat. The choice only affects the weight coefficients in this table, but the implication is that these three fluxes are not proportional to each other in the context of the DEB theory as well as in the context of indirect calorimetry. The numerical behaviour

<table>
<thead>
<tr>
<th>Intra-species</th>
<th>Inter-species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</td>
<td>( \propto L_g L^2 + L^3 )</td>
</tr>
<tr>
<td>Growth</td>
<td>( \propto L_g L^2 - L^3 )</td>
</tr>
<tr>
<td>Structure</td>
<td>( \propto L^0 )</td>
</tr>
<tr>
<td>Respiration</td>
<td>( \propto L_g L^2 + L^3 )</td>
</tr>
<tr>
<td>Weight</td>
<td>( \propto d_v L^2 + d_v L^3 )</td>
</tr>
</tbody>
</table>
of both the intra- and the interspecific relationship is remarkably close to the well-known observation by Kleiber [19] that respiration scales with body weight$^{3/4}$.

### 3.1 Empirical body size scaling relationships

Respiration has empirically been found to be proportional to the body weight to the power percentage in animals [19]. Many attempts have been made to explain this, but only the explanation offered by the DEB theory survived criticism [33]. A detailed discussion is beyond the scope of this paper, but one of the flaws of most alternatives is that they fail to make a sharp distinction between intra- and inter-species scaling relationships. When an organism grows from young and small to old and large, its parameters remain fixed, but its metabolic behaviour changes with the state variables (size). Small ones, for instance, invest much more in growth than larger ones and the overhead costs of growth appear in the respiration rate. An adult mouse and an adult elephant, however, both do not grow, and they differ in parameter values. The error of not distinguishing between intra- and inter-species comparisons is easy to make, because the numerical behaviour is rather similar (cf. table 2), but the explanation is very different. DEB theory demonstrates that respiration has contributions from various metabolic processes, and each of these contributions should be considered. Most other attempts to explain body size scaling relationships do the opposite: they consider respiration as the basic quantity, and try to explain all other ecophysiological processes by linking them to respiration in one way or another. Others, such as [24], make a plea for not even trying to explain scaling relationships.

Recently, the respiration of plants was found to be proportional to weight (to the power one, rather than $3/4$) [34], and the authors argue that this makes plants fundamentally different from animals. They selected saplings and seedlings in the weight range of 0.01–10,000 g of a few tree species. The adult size of these trees, however, is not very different, meaning that their parameter values are also not very different. So their comparison is basically an intra-species comparison of individuals that weigh just a tiny fraction of the fully grown ones. DEB theory correctly predicts that in this case we should expect that respiration is proportional to weight [11]. This is because in the early life stages plants behave as V1-morphs (i.e. they change in shape during growth such that their surface area is proportional to their volume), which implies that they grow exponentially (so proportional to their mass), while assimilation and maintenance are proportional to their mass as well. The conclusion must be that these data do not support a fundamental difference between plants and animals, but that we need the appropriate theoretical framework to recognise this. A problem with woody plants is, however, that wood is a product that sticks to the plant, but is not metabolically active while its contribution to weight is substantial. As long as plants behave as V1-morphs, this affects the value of the proportionality constant. A more subtle comparison of these data with that of animals should account for wood; the metabolism of living cells of plants and animals have many similarities, as is well known.

When the incubation times of eggs of birds are plotted log-log against egg weight, the tubenoses (e.g., albatrosses, petrels, shearwaters) show exceptionally long incubation times, but otherwise the slope of the regression line is not too different from the expected value $1/4$. Using DEB theory, the reason for this can be traced back to the fact that their relative eggs size is exceptionally large. The ecological functionality is
that a large egg goes with a short period on the nest, so a short period in which the birds
are bound to a particular island, which limits their possibilities for foraging. This seems
counter-intuitive at first sight, because larger eggs go with long incubation times in
inter-species scaling. Intra-specifically, however, when all parameters are kept fixed
except relative egg size, the reverse applies [11]. This type of analysis is only possible
with theory behind the scaling relations.
The complete specification of the standard DEB model is beyond the scope of this paper,
and its implications easily cover a book [11]. The standard model can be and has been
extended into different directions: Changes in shape during growth can be taken into
account, more types of reserve (required for autotrophs) and of structure (required for
plants) can be delineated, more nutritional “details”, adaptations, tumour growth, etc.
The evolutionary aspects of such extensions are discussed in [35, 36].

4. Interactions between QSPRS and body size scaling relationships

Body size affects chemical kinetics in rather complex ways, so do changes in body size.
Since DEB theory is about the dynamics of body size, this directly points to the
importance of the link between DEB theory and toxico-kinetics. Here, we briefly
review some pertinent items; each of these items can be discussed in much more
detail, but this would involve more details of the DEB theory, which is beyond the
scope of this paper. It is useful to start with an inventory of the possible uptake
and elimination routes of the compounds under consideration, and then consider
other chemical and metabolic aspects.

_Uptake_ can be directly from the environment, which is proportional to the surface
area of individuals. The implication is that elimination rates are inversely proportional
to length. So the time it takes to saturate an organism with a chemical compound is
proportional to its (volumetric) length. Uptake can also be via food, and food
uptake scales with surface area intra-specifically, but with volume inter-specifically.

_Dilution_ by growth matters, even at low growth rates. The growth rate depends on the
size of the individual, relative to the maximum size, so intra- as well as inter-specific
scaling relationships contribute.

_Elimination_ can be directly to the environment (involving the surface area), and/or to
the gut contents (involving the feeding rate), and/or via reproduction or some other
species-specific routes. The possible significance of the latter route is obvious from
the observation that a female adult daphnid can produce offspring at the rate of
25% of her own weight per day. If chemical compounds are in eggs at formation,
this can represent an important elimination route. The reproduction rate (in number
of offspring per time) is proportional to a weighted sum of surface area and volume
intra-specifically, and inversely proportional to a length inter-specifically. Since the
mass per offspring is proportional to volume, allocation to reproduction is proportional
to surface area inter-specifically. We hasten to add that the relative size of offspring is a
lot more species-specific (so subjected to evolutionary adaptation) than the allocation to
reproduction [11, 37, 38].

The _chemical composition_ of biomass also depends on size, since the reserve density
(the ratio of the amounts of reserve and structure) is constant intra-specifically, but
proportional to a length inter-specifically. Reserve might be more rich in lipids than
structure (depending on the taxa that are studied). This observation obviously matters for the comparison of compounds that differ in $P_{ow}$.

Chemical transformation in an organism is linked to the metabolic activity of the organism, and obviously depends on the properties of the chemical and of the organism. Lipophilic compounds are frequently transformed into less lipophilic ones, which enhances excretion (elimination). These metabolites are, frequently, more toxic. Moreover, uptake and elimination frequently involve metabolic activity. The standard DEB model specifies all metabolic activities, and the rate at which reserves are mobilised seems to be the best candidate to link with (the potential for) metabolic transformation and excretion. It has close links with the respiration rate, as a quantifier for metabolic activity.

A further modification of the role of metabolic transformation in the toxicity of compounds is when the effects are receptor-mediated [39]. The turnover rate of receptors is possibly linked to the somatic maintenance process, in which case the specific turnover rate is independent of body size, but it might also be linked to the metabolic activity. We still need more experience with the application of receptor-mediated models. The observation that effects are linked to the product of concentration and exposure time motivated many toxicologists to think about the involvement of receptors, although their biochemical identification remained uncertain. This motivation is incorrect, however, if the hazard rate is linear in the (internal) concentration. This is because even without receptors the effect on the survival probability is already via the product of concentration and exposure time. The significance of receptors is in the contribution of the exposure history in the effect, rather than of the actual exposure. This requires an in-depth analysis of how effects build up in time and imposes strong constraints on the quality of data. It is only by analyzing multiple endpoints simultaneously that we found indications that the effects of organophosphorus esters on fish involve receptors [39].

These considerations require a second thought about the effects of chemicals. As long as lipophilic compounds are accumulated in metabolically rather inactive lipids, they are less likely to have metabolic effects. Many animals, and especially mammals, have tissues (the adipose tissue) that are specialised in the storage of such lipids. As soon as these lipids are used, however, effects might show up. This calls for a much more dynamic view on the effects of chemicals, and links up with traditions in pharmaco-kinetics and medical research on the effects of chemicals.

5. Tertiary scaling relationships

Both QSPRS and body size scaling relationships concern primary model parameters. Many ecophysiological processes can be written as functions of these parameters. Evaluations of how these functions depend on $P_{ow}$ or maximum body size are called secondary scaling relationships [11]. When the relationships involve the population level, interactions between individuals, we call them tertiary scaling relationships, such as average home range, population densities, specific population growth rates. They are of a much weaker type, but also more relevant to the ecosystem, and so to risk assessment [40].

The DEB theory is especially designed for linking properties of individuals to that of populations, in combination with the theory for physiologically structured
population dynamics [41], which can be seen as an advanced book-keeping tool to work out population performance, given a specification of the performance of individuals. So, the consequences of changes in these properties (by toxic compounds, or by evolution) can be evaluated at the population and ecosystem level in the context of the DEB theory. To this end, the specification of how individuals interact with their environment should be extended to include interactions (e.g., competition for food, syntrophic or predator-prey interactions) and physical and chemical processes that are pertinent to this organisation level.

Using this framework for linking the two levels of organisation, effects of $P_{ow}$ and body size can be evaluated at the population level, including accumulation and effects in food webs. This makes the whole exercise more relevant in the context of environmental risk assessment, which is the main motivation behind the scientific interest in effects of chemical compounds on organisms. The public concern is about the quality of the environment as a whole, which has complex relationships with the fate of individuals.

6. Discussion and conclusions

Both the one compartment and the standard DEB model are about the uptake of chemical compounds from the environment by an organism. The one compartment model does not consider transformation, only elimination. The standard DEB model only considers transformation, not elimination; active excretion is inherent to multi-reserve systems not single-reserve ones, though faeces, carbon dioxide and nitrogen-waste production and dioxygen consumption are also basic to the standard DEB model. The purposes of both models are quite different, yet they share the intriguing property that scaling relationships are implied by the structure of the models.

A further intriguing observation from the DEB model is its invariance property: two individuals with different parameters, but the same amounts of structure and reserve, behave identically in the same constant environment if their parameters differ in a special way. As soon as the environment changes, the individuals will differ in amounts of structure, reserve and/or offspring, but not as long as the environment remains strictly constant. One subset of parameters must be identical, and another subset can differ by the same but arbitrary common factor [11]. Except for the searching rate and the life-stage parameters (length at birth and puberty) this results in exactly the same relationship as found for the body-size scaling relationship. This time, however, the physical interpretation of the parameters (and state variables) is not used; the result is purely mathematical. This probably relates to something deep in the nature of physical dimensions.

We briefly discussed some shortcomings of empirical approaches to QSPRS and body size scaling relationships. They share the property that the popular application of linear regression to log-transformed data hardly makes sense, because the reason why a particular data point deviates from the deterministic line is not the result of a random trial from some probability density function. Although the uncertainty of a particular data point might be substantial, if a particular compound is more toxic than the line predicts, a repetition of that measurement will probably confirm this extra toxicity. Regression models have their origin in physics, where the (typically small) deviation from the deterministic model component is interpreted
as measurement error. The formal definition of this error is that if we take the mean value of an increasing number of repeated measurements, the deviation from the deterministic value disappears. This interpretation does not apply in the scaling relationships. This means that any statistical evaluation that is based on this unrealistic model must not be taken too seriously.

QSPRS and body size scaling relationships are about the covariation of parameter values of models when applied to different data sets. The way parameter values should covary can be deduced from the model structure, without using any empirical argument. An important practical implication is that if toxicity parameters and the $P_{ow}$ of one compound is known, and the $P_{ow}$ of a physiologically related compound, the toxicity parameters of that second compound can be predicted. There is no longer a need to delineate a large class of related compounds, assemble a lot of toxicity data and apply regression techniques; such techniques have several drawbacks anyway. Similarly, if the parameters of a particular species are known, and the maximum body length of a second species, the parameters of the second species can be predicted.

This approach only applies to special models, the one-compartment model for toxicokinetics and the standard DEB model for energetics. These models share the property that the partition coefficient and the ultimate length, respectively, can be expressed as a ratio of two rate parameters. Since body size and metabolic activity affect toxicity in a profound way, QSPRS and body size scaling relationships are natural partners in the understanding of toxicity (and pharmacological) patterns.

Acknowledgments

This research has been supported financially by the European Union (European Commission, FP6 Contract No. 003956 and No. 511237-GOCE) and the Netherlands Technology Foundation (STW), grant WEB.5509.

References
