DEBtox background, theory and models

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Model versions

The term 'DEBtox' was coined in 1996 for the user-friendly software that contained a set of simplified model equations to analyse standard toxicity data (Kooijman and Bedaux, 1996a). It featured a hazard model for survival (equivalent to current GUTS-RED-SD), simplified DEB models for fish growth and Daphnia reproduction, and an exponential algae population growth model. Since then, the meaning of the term 'DEBtox' has become a bit confused, and often broadened to encompass all DEB-based models used to analyse/predict toxicant stress. All the models that have been presented/applied in the literature are closely related, but still different enough to be confusing, and different enough to have different data needs. The sections below explain the major categories of DEBtox models.

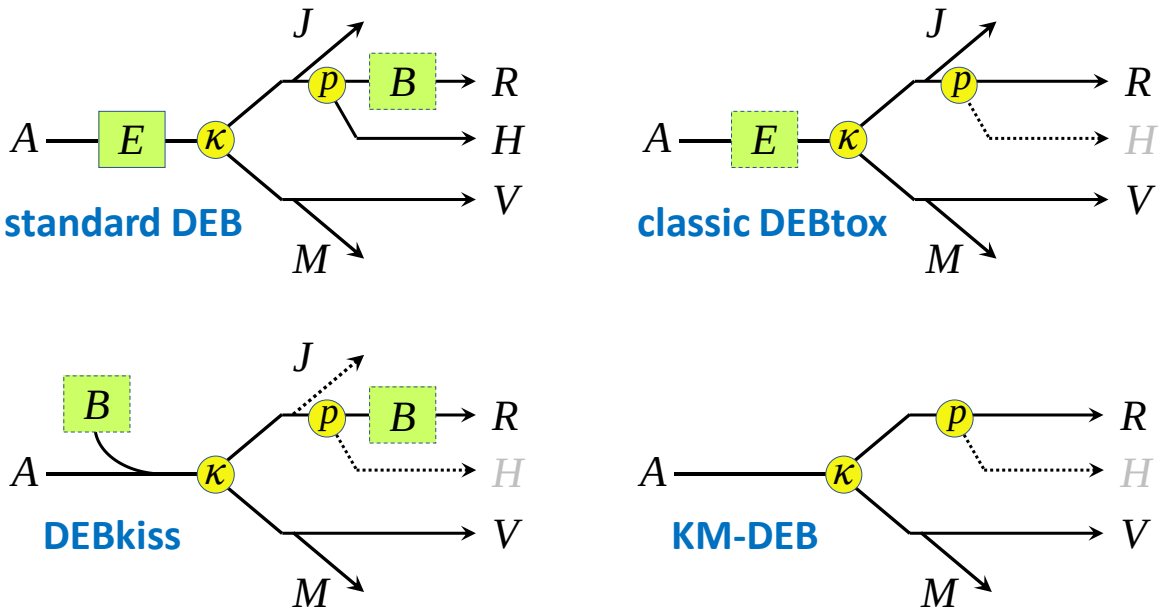

Figure 1. Schematic representation of the resource flows in various DEB versions. *A* = assimilation, *M* = somatic maintenance, *J* = maturity maintenance (optional in DEBkiss, but usually included), *V* = structural biomass, *R* = reproductive output (gametes). *H* = maturity (generally not explicitly followed in simplified versions; however, it is needed to allow for a constant *κ*). The allocation fraction *κ* splits the resource flow between the soma and maturation/reproduction; the split *p* marks 'puberty' (start of investment into gametes). *E* = reserve (absent in DEBkiss and KM-DEB), *B* = resource buffer: an optional reproduction buffer (for DEBkiss, there is also an egg buffer that is used for embryos only).

Classical DEBtox

What is it. Model equations phrased in simple compound parameters (maximum length, von B. growth rate constant, etc.). Reserve included but simplified to immediate steady state with the food availability (no reserve dynamics), and not included in body size. Stage transitions (i.e., puberty) triggered by a fixed body size. Effects are linked to the (scaled) internal concentration. Toxicokinetics includes scaling of the elimination rate by surface:volume ratio and dilution of internal concentrations by body growth. Classical DEBtox considers as pMoAs: assimilation/feeding, maintenance (somatic

and maturity together), growth costs, costs for reproduction, and hazard to reproduction. In several publications, a combined cost for growth and cost for reproduction was used.

Track record. This version has a long history in ecotoxicological research, with rather minor modifications over the years. Most of the entries collected in the list of publications at my website (http://www.debtox.info/papers_debtox.html) have used classical DEBtox (with minor modifications).

Key publications. Kooijman and Bedaux (1996a), Kooijman and Bedaux (1996c), Kooijman and Bedaux (1996b), Jager *et al.* (2004), Billoir *et al.* (2008), Jager and Zimmer (2012) (this latter publication also specifies how to include scaled reserve dynamics in the model).

Standard DEB

What is it. Model equations phrased strictly in primary parameters (maximum area-specific assimilation rate, volume-specific maintenance costs, kappa, etc.). Reserve included dynamically, and also included in body size. Stage transitions (birth, puberty) are linked to the cumulative investment into maturity rather than body size. This model version does not have a dedicated effects module. In the few cases where this model has been used to fit toxicity data, ad hoc effect modules were used, or the same module as for classical DEBtox (ignoring the impact of reserve on TK).

Track record. Only very few published case studies where data for growth and reproduction are fitted under toxicant stress. More recently, two publications for early life stages of fish. However, this model has a large track record *outside* of ecotoxicology.

Key publications. Kooijman (2010), Sousa *et al.* (2008), Augustine *et al.* (2012), Baas *et al.* (2018), Zimmer *et al.* (2018).

Scaled standard DEB

What is it. Exact same model as standard DEB, but scaled with the maximum area-specific assimilation rate. This removes the dimension of 'energy' from the system, which facilitates practical application. However, this means that a number of primary parameters are turned into abstract compound ones (e.g., the specific somatic maintenance cost is turned into a somatic maintenance rate *coefficient* with dimension 'per time'). This model version also does not have a dedicated effects module. In the few cases where this model has been used to fit toxicity data, the same module as for classical DEBtox has been used (ignoring the impact of reserve on TK). A somewhat more extensive set of pMoAs was defined (Jager *et al.*, 2010), including effects on kappa.

Track record. Only very few published case studies where data for growth and reproduction are fitted under toxicant stress. Note that DEB-IBM, as developed by Ben Martin, also uses the scaled standard model.

Key publications. Kooijman *et al.* (2008), Jager *et al.* (2010), Jager and Selck (2011), Martin *et al.* (2013).

Standard DEBkiss

What is it. Model equations phrased in terms of primary parameters (maximum area-specific assimilation rate, volume-specific maintenance costs, kappa, etc.). All resource flows specified in mass rather than energy. Reserve *excluded* explicitly, though a reproduction buffer can be used. Stage transitions (i.e., puberty) triggered by a fixed body size, though a state variable for maturity can easily

be included. Maturity maintenance can be included or excluded without extra parameters (by assuming a relationship to somatic maintenance, as also used in classical DEBtox). This model version does not have a dedicated effects module, though a number of options have recently been worked out in the DEBkiss e-book.

Track record. There are a number of publications with DEBkiss (see list at http://www.debtox.info/debkiss_appl.html), although only a few dealing with toxicant stress.

Key publications. Jager *et al.* (2013), Barsi *et al.* (2014), Jager (2018).

DEBtox2019 (DEBkiss-based DEBtox)

What is it. The standard DEBkiss model (including maturity maintenance) has been simplified and phrased in simple compound parameters (maximum length, von B. growth rate constant, etc.), just like the classical DEBtox model. This yields a basic model (everything not dealing with toxicants) that is *very* similar to the classical DEBtox model; in fact, it can be viewed as a special case of the classic model, where the reserve compartment is infinitely small (parameter g goes to infinity, and completely drops out), and where absolute body length is used rather than scaled length. The basic model is also very similar to the earliest DEB version (Kooijman and Metz, 1984), which has been applied by Klok and co-workers (e.g., Klok and De Roos, 1996; Klok, 2008) in ecotoxicology. The Kooijman-Metz version has no reserve and also does not consider maturity maintenance.

The lack of reserve makes this model version easier to use (one parameter less), but also means that a consistent starvation module can be added (for the classical DEBtox this would be impossible to do in a consistent manner). The toxicant module of this model version is not entirely crystallised yet, but is currently phrased in a very flexible manner such that it can be configured in many ways (discussed in more detail later). Effects are explicitly linked to scaled *damage* (as in GUTS).

Track record. The basis of this model version was derived in 2018 and presented in the DEBkiss e-book; a publication with a more worked-out version was submitted in 2019. It therefore has no track record yet, but since its basic model is very similar to classical DEBtox and Kooijman-Metz DEB, it can lean of the track record of those versions.

Key publications. Jager (2018), Jager (subm.).

Which model version to take?

The EFSA Scientific Opinion on TKTD modelling (EFSA, 2018) does not choose between the different model versions, and mentions classical DEBtox, standard DEB, and DEBkiss. Of course, the first question would be: do we *need* to choose? It is possible to use different model versions for different types of data sets, or for different types of questions. However, for regulatory purposes it would be advantageous to focus on one model version, to minimise confusion among users, minimise ambiguity in decision making, and to allow for efficient and focussed guidance on model use and interpretation.

The question on which version to take has two elements: which basic DEB model to use, and which effects module to use.

Which DEB model to use?

In terms of the DEB model to use, all versions are very closely related, and it is unlikely that they will lead to biologically/toxicologically-relevant different conclusions (this is e.g., supported by a comparison of three versions in Jager and Klok, 2010). In fact, I expect these differences to be completely dwarfed by the impact of the selection of modules for TK/damage representation,

biotransformation, reproduction buffer, etc. The choice of whether to include a reserve is likely most relevant when starvation plays a role (either because food levels fluctuate, or because assimilation or maintenance rates are affected by a time-varying toxicant stress). However, an animal's response to (severe) starvation rests on so many biological aspects that it is unlikely that any DEB model version can be called 'superior'. For example, it is likely that organisms can use their reproduction buffer to pay maintenance costs, but such a buffer has so far (to my knowledge) always been excluded from ecotox applications of DEB. Furthermore, it is not so clear to what extent structural biomass can be used, and to what extent maintenance costs are reducible under starvation. However, it is good to stress that the classical DEBtox can be called 'inferior' in this respect as it cannot deal consistently with starvation at all. This is important for ERA of pesticides, as time-varying exposure may induce starvation, even among well-fed individuals.

The five model categories explained above can be placed along two axes: simplified-full and primary-compound (Fig. 2). Since we should not expect meaningful differences between the model versions, the choice can be made on practical grounds. For ERA application, it may be sufficient to reduce the choice to the extreme edges of the diagonal in Figure 2: either go for a complete standard DEB model in compound parameters, or for the most simplified DEB model in compound parameters. Some differences between these two strategies are presented in Table 1.

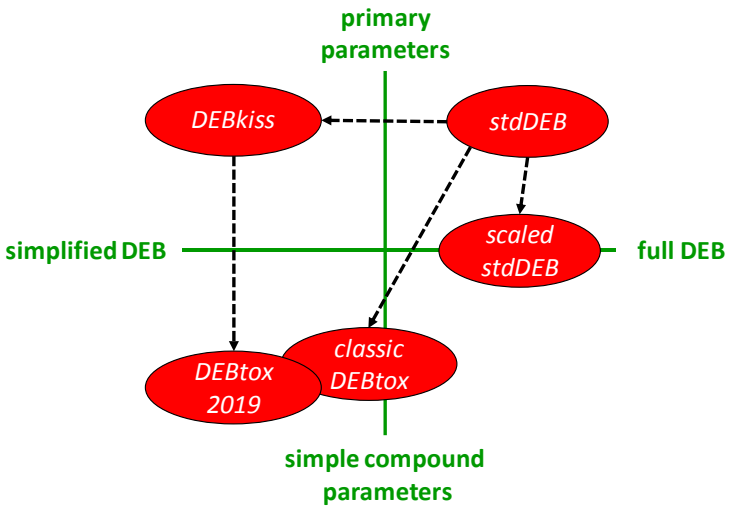

Figure 2. Placement of the five model version along two axes. Broken arrows indicate derivations.

Table 1. Differences between the two extremes in Figure 2.

	Standard DEB	**DEBtox2019 (DEBkiss-based)**
Transparency	Model will have to be used as a 'black box' in ERA (more similar to how fate models are used). Parameters can hardly be interpreted since they have 'energy' in their dimensions. Very different parameterisations can lead to very similar model fits. Model equations are rather tough, and difficult to implement (especially the 'maternal effects rule', which is therefore often simply ignored).	The model can be applied in a similar way to the GUTS model. Simple model equations, with simple-to-interpret parameters. Can easily be implemented (even in Excel, with some effort).
Calibration	Can make use of large library with parameter values for many species (AmP). However, AmP entries differ in quality, 'pseudo data' are used to augment available data, and the generic entry for a species may not describe the controls in a specific test well (requiring some form of tweaking).	Does not need AmP: the basic parameters can be obtained from the toxicity test itself, as long as body size and reproductive output are determined over time.
Status	Large user community, many publications (though very few in ecotoxicology). There is a substantial organisation in place (Wiki, symposium, AmP, course).	This model version is very new. However, the basic model is extremely similar to classical DEBtox, which has a large user community and many publications.

Courses	International DEB course (once every two years), linked to the DEB symposium.	DEBkiss is used in the summer school on TKTD modelling (once every two years).
Realism	Potentially more biological realism. However, the areas of more realism (reserve, maturity) are also the most uncertain (both in terms of conceptual validity and of correct parameterisation). The 'maternal effects rule' is actually invalid for many species (e.g., Daphnia).	Potentially less realistic due to its simplifications (lack of reserve, body size as maturity proxy), though clearly capable of explaining the patterns in many toxicity tests (with the data sets that have so far been used).
Early life	Can deal with early life stages, though TK in eggs and yolk-sac larvae needs further study (in current examples, the yolk sac is simply ignored for TK).	Likely cannot deal with early life stages. The full DEBkiss model in primary parameters *can*, but the simplification to easy compound parameters probably precludes modelling early-life stages.
Expandability	Can be expanded with various modules such as different starvation strategies, reproduction buffer, effects on kappa, etc. However, adding a consistent TK module is complicated by the presence of a reserve.	A consistent TK module is easy to add, due to the lack of reserve. Other expansions (e.g., repro buffer and effects on kappa) are more problematic, mainly because of the formulation in compound parameters. The full DEBkiss does not have this limitation, but also shares some of the disadvantages with standard DEB (e.g., cannot be calibrated on toxicity data alone).

Which effects module to use?

The classical DEBtox scheme is shown in Figure 3, with effects being driven by scaled internal concentrations. One thing that should be made very clear is that the 'standard' effects module used for DEBtox should *not* be used anymore. The recent developments in the GUTS framework (Jager and Ashauer, 2018) have clearly established that 'damage' should be considered explicitly, as driver of toxicity. Almost always, there will be no information on TK when applying DEBtox. So, what's wrong with using the model for 'scaled internal concentrations' of classical DEBtox? Scaled internal concentrations were used in the hazard model of the classical DEBtox software, which is mathematically equivalent to the modern GUTS-RED-SD: even though some state variables and parameters have a different name (and different interpretation) the model fits and model predictions will be the same.

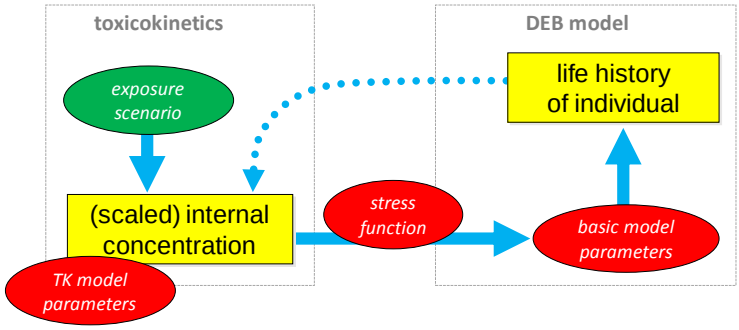

Figure 3. Schematic representation of the classical DEBtox model, where effects are driven by scaled internal concentrations. Dotted arrow represents feedbacks (effects of growth on TK).

The crucial difference between DEBtox and GUTS lies in the feedbacks for TK. In contrast to GUTS, DEBtox animals will grow and reproduce, and this will affect TK. Classical DEBtox considered dilution of the internal concentration by growth, and scaling of the rate constants with surface:volume ratio, as feedbacks (but not losses with reproduction). This makes sense for body residues, but these processes are not so obvious when damage dynamics dominate. Furthermore, scaling with surface:volume ratio will generally be a bad idea when TK is driven by biotransformation. These

complications have so far been ignored by the DEBtox community by assuming that toxicity is always driven by the scaled internal concentration of the parent compound. These feedback processes have quite an impact on the parameter estimates, and thereby also on extrapolations to different exposure scenarios (especially time-varying exposure) and different environmental conditions (e.g., food limitation). In fact, it is likely that the correct identification of these feedbacks is way more important than the choice between various basic DEB models.

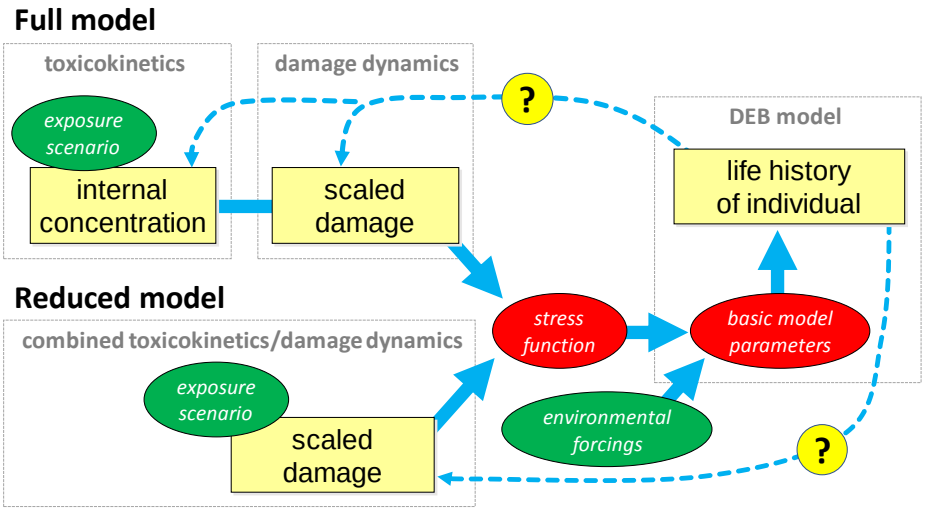

Figure 4. Schematic representation of the updated DEBtox model, where effects are driven by scaled damage, and a distinction is made in a full and reduced model. Broken arrows represent potential feedbacks (effects of growth and possibly reproduction on TK and possibly on damage dynamics). Parameters for TK and damage dynamics not shown.

It is almost impossible to know *a priori* which feedbacks are relevant for a species-chemical combination. Standard toxicity tests at constant exposure do not provide enough information to make an informed decision. However, it is likely that experiments with pulsed exposure *can* provide the necessary information. Up till now, these experiments have not been performed (in any case not published), apart from one study (Pieters *et al.*, 2006) with a single pulse at the start of the experiment (which is not helpful to distinguish between various feedback options).

The discussion on the most appropriate TK/damage module is largely independent of the choice of basic DEB model: there is no reason to take a different module for different DEB model versions. However, it is good to realise that, for standard DEB, the reserve compartment provides an additional complication: in a consistent TK module, the reserve (and its dynamics) should be accounted for. This raises several new questions, such as: does the reserve contribute to the surface area for uptake, and what is the affinity of the chemical for reserve, relative to structure? These questions are discussed, and some options worked out, in the technical document for the DEBtox e-book (Jager, 2019).

For the feedbacks, I propose a flexible setup that can be configured in various ways (Jager, subm.). At this moment, there is simply not enough detailed experimental work performed to shed light on the most representative option (which likely depends on the chemical and the species as well).

Feedback configuration	**scaling of uptake rate**	**scaling of elimination rate**	**dilution by growth**	**losses with reproduction**
Full feedbacks	1	1	1	1
Classic DEBtox	1	1	1	-
Diluted damage	-	-	1	-
Non-diluted damage	-	-	-	-

Metabolite driving toxicity	-	1	1	?
…				

Similarly to the feedbacks, I also propose to configure the mode of action in the same manner. This is not substantially different from the classical DEBtox model but makes it easier to combine various modes of action. Note that I ignored the classical "hazard to the embryo" pMoA from this list; I never found a convincing case of this one, and the repro costs pMoA will act almost identically.

pMoA configuration	**Assimilation/ feeding**	**Maintenance costs**	**Growth costs**	**Repro costs**
Assimilation	1	-	-	-
Maintenance	-	1	-	-
Assim.+maint.	1	1	-	-
Growth costs	-	-	1	-
Repro costs	-	-	-	1
Growth+repro	-	-	1	1
…				

Way forward

The number of options in the effects module is rather large. At this moment, there is a huge lack of detailed experimental studies to help with these choices. It is highly likely that studies combining constant and pulsed exposure will shed more light on the most-useful configurations (but there are no published case studies with such a setup yet). In the longer term, we should be able to prune the number of options, or design rules for the most-relevant configuration for a given group of chemicals in a certain (group of) species. In view of the considerable uncertainties in the effects module, I personally think it is prudent to start working with the simplest possible DEB model.

Other issues that need attention:

- Statistical framework. Currently, DEBtox models are fitted to data assuming independent and normally distributed (after transformation) residuals, and independence of the various traits. This is a rather crude approximation, but alternatives are not in sight.
- DEBtox fitting/simulation requires numerical ODE solvers, and the model is particularly tough on those solvers. Fitting strategy also needs attention as fitting all parameters of a DEBtox model (generally 8 or more) simultaneously is a bad idea.

References

Augustine, S, B Gagnaire, C Adam-Guillermin, SALM Kooijman (2012). Effects of uranium on the metabolism of zebrafish, *Danio rerio*. *Aquatic Toxicology* **118**: 9-26.

Baas, J, S Augustine, GM Marques, JL Dorne (2018). Dynamic energy budget models in ecological risk assessment: From principles to applications. *Science of the Total Environment* **628-629**: 249-260.

Barsi, A, T Jager, M Collinet, L Lagadic, V Ducrot (2014). Considerations for test design to accommodate energy-budget models in ecotoxicology: a case study for acetone in the pond snail *Lymnaea stagnalis*. *Environmental Toxicology and Chemistry* **33**(7): 1466-1475.

Billoir, E, ML Delignette-Muller, ARR Péry, O Geffard, S Charles (2008). Statistical cautions when estimating DEBtox parameters. *Journal of Theoretical Biology* **254**(1): 55-64.

EFSA (2018). Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms. *EFSA journal* **16**(8): 5377.

Jager, T (2018). *DEBkiss. A simple framework for animal energy budgets*. Version 2.0, 15 November 2018, Leanpub, https://leanpub.com/debkiss_book.

Jager, T (2019). *Making sense of chemical stress. Applications of Dynamic Energy Budget theory in ecotoxicology and stress ecology*. Version 2.0, 9 May 2019, Leanpub, https://leanpub.com/debtox_book.

Jager, T, R Ashauer (2018). *Modelling survival under chemical stress. A comprehensive guide to the GUTS framework*. Version 2.0, 8 December 2018, Toxicodynamics Ltd., York, UK. Available from Leanpub, https://leanpub.com/guts_book.

Jager, T, T Crommentuijn, CAM Van Gestel, SALM Kooijman (2004). Simultaneous modeling of multiple endpoints in life-cycle toxicity tests. *Environmental Science & Technology* **38**: 2894-2900.

Jager, T, C Klok (2010). Extrapolating toxic effects on individuals to the population level: the role of dynamic energy budgets. *Philosophical Transactions of the Royal Society B-Biological Sciences* **365**: 3531-3540.

Jager, T, BT Martin, EI Zimmer (2013). DEBkiss or the quest for the simplest generic model of animal life history. *Journal of Theoretical Biology* **328**: 9-18.

Jager, T, H Selck (2011). Interpreting toxicity data in a DEB framework: a case study for nonylphenol in the marine polychaete *Capitella teleta*. *Journal of Sea Research* **66**: 456-462.

Jager, T, T Vandenbrouck, J Baas, WM De Coen, SALM Kooijman (2010). A biology-based approach for mixture toxicity of multiple endpoints over the life cycle. *Ecotoxicology* **19**: 351-361.

Jager, T, EI Zimmer (2012). Simplified Dynamic Energy Budget model for analysing ecotoxicity data. *Ecological Modelling* **225**: 74-81.

Klok, C (2008). Gaining insight in the interaction of zinc and population density with a combined dynamic energy budget and population model. *Environmental Science & Technology* **42**: 8803-8808.

Klok, C, AM De Roos (1996). Population level consequences of toxicological influences on individual growth and reproduction in *Lumbricus rubellus* (Lumbricidae, Oligochaeta). *Ecotoxicology and Environmental Safety* **33**: 118-127.

Kooijman, SALM (2010). *Dynamic energy budget theory for metabolic organisation*. Cambridge, UK, Cambridge University Press.

Kooijman, SALM, JJM Bedaux (1996a). *The analysis of aquatic toxicity data*. Amsterdam, The Netherlands, VU University Press.

Kooijman, SALM, JJM Bedaux (1996b). Analysis of toxicity tests on *Daphnia* survival and reproduction. *Water Research* **30**(7): 1711-1723.

Kooijman, SALM, JJM Bedaux (1996c). Analysis of toxicity tests on fish growth. *Water Research* **30**(7): 1633-1644.

Kooijman, SALM, JAJ Metz (1984). On the dynamics of chemically stressed populations: the deduction of population consequences from effects on individuals. *Ecotoxicology and Environmental Safety* **8**: 254-274.

Kooijman, SALM, T Sousa, L Pecquerie, J Van der Meer, T Jager (2008). From food-dependent statistics to metabolic parameters, a practical guide to the use of dynamic energy budget theory. *Biological Reviews* **83**: 533-552.

Martin, BT, T Jager, RM Nisbet, TG Preuss, M Hammers-Wirtz, V Grimm (2013). Extrapolating ecotoxicological effects from individuals to populations: a generic approach based on Dynamic Energy Budget theory and individual-based modeling. *Ecotoxicology* **22**: 574-583.

Pieters, BJ, T Jager, MHS Kraak, W Admiraal (2006). Modeling responses of *Daphnia magna* to pesticide pulse exposure under varying food conditions: intrinsic versus apparent sensitivity. *Ecotoxicology* **15**: 601-608.

Sousa, T, T Domingos, SALM Kooijman (2008). From empirical patterns to theory: a formal metabolic theory of life. *Philosophical Transactions of the Royal Society B-Biological Sciences* **363**(1502): 2453-2464.

Zimmer, EI, TG Preuss, S Norman, B Minten, V Ducrot (2018). Modelling effects of time-variable exposure to the pyrethroid beta-cyfluthrin on rainbow trout early life stages. *Environmental Sciences Europe* **30**.