Challenges related to application of DEBtox modelling in regulatory ERA

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Background: The EFSA scientific opinion on TKTD modelling

The basic idea of regulatory evaluation of model applications for use in environmental risk assessment as laid down in the EFSA TKTD SO is to avoid an overload of regulators related to the submission of modelling dossiers. This because the thorough evaluation of modelling dossiers need some level of mathematical and programming education and/or experience, and these skills are not (yet) so frequently found at regulatory authorities. The workload for evaluators of DEBtox model applications working in authorities can be reduced by preparing a structured report with standard elements, like it was already suggested in the EFSA SO on Good Modelling Practice (EFSA PPR 2014), and is based on model documentation protocols such as ODD (Grimm et al., 2010) and TRACE (Grimm et al., 2014).

The EFSA scientific opinion on TKTD modelling (EFSA PPR 2018) used this approach for developing reporting formats but went one step further. Since GUTS models have a standardised theory, the TKTD scientific opinion (SO) could provide evaluations for some of the elements required in a standard modelling dossier format for GUTS, i.e. for the conceptual model, the formal (mathematical model), model implementations, sensitivity analysis, and the environmental scenario. Also, the SO works out method explanations for calibration and validation of the GUTS models, including the provision of concrete quality criteria. In addition, the propagation of uncertainty to model results was explained and concrete options for respective calculations were given. Altogether, the formulation of standardised modelling dossier elements, the generic evaluation of some of these elements for standardised parts of the models, and the formulation of explanations and quality criteria for the aspects which remain to be evaluated per model application for a concrete dossier, created a template for GUTS model applications for the regulatory risk assessment which intend to minimise the effort for evaluators and maximise transparency and scientific rigidity.

First aim: Agree on standardised modelling approach for effects of chemicals on growth and reproduction

The TKTD SO formulated similar ideas also for the application of DEBtox models, but a concrete evaluation of standardised elements and more specific explanations how model calibration and validation could be assessed and evaluated was not possible, amongst others for the following reasons:

- Due the lack of a really standardised model theory the conceptual and formal model could not be evaluated
- Because of a missing standard model and the lack of an accessible software implementation model implementations could not be tested and sensitivity analyses could not be performed
- Aspects of the scenario, of propagation of uncertainty to model results, and of the use of DEBtox results in the tiered aquatic risk assessment scheme were discussed, but no concrete options were derived due to the lack of examples.
- The preliminary suggestion in the TKTD SO was to follow the route which was given for the GUTS model, i.e. to use a constant environmental scenario according to the lab results, and to follow also the approach to propagate uncertainty to the model result. These suggestions need, however, further work and provision of examples.

Because of the limitations the lack of a consistent theory pose towards the use of these model sin regulatory RA, the first step for the DEBtox workshop needs to be achieving agreement or at least some common understanding of the theory behind applications of the DEB theory for analysing questions in context of the regulatory risk assessment of chemicals. This is the aim for (roughly) day 1 of the workshop.

Second aim: identify consequences of the chosen modelling approach for regulatory evaluation

Based on a (preliminary) idea of a possible standardised DEBtox approach, the second part (day) of the workshop will find some time for discussions on the perspective of regulators on the DEBtox development, and to discuss and identify consequences of for RA. Especially the question whether regulatory evaluation needs to consider a separate evaluation of physiological (DEB) model parts or can focus on calibration of simplified and targeted models will need to be analysed.

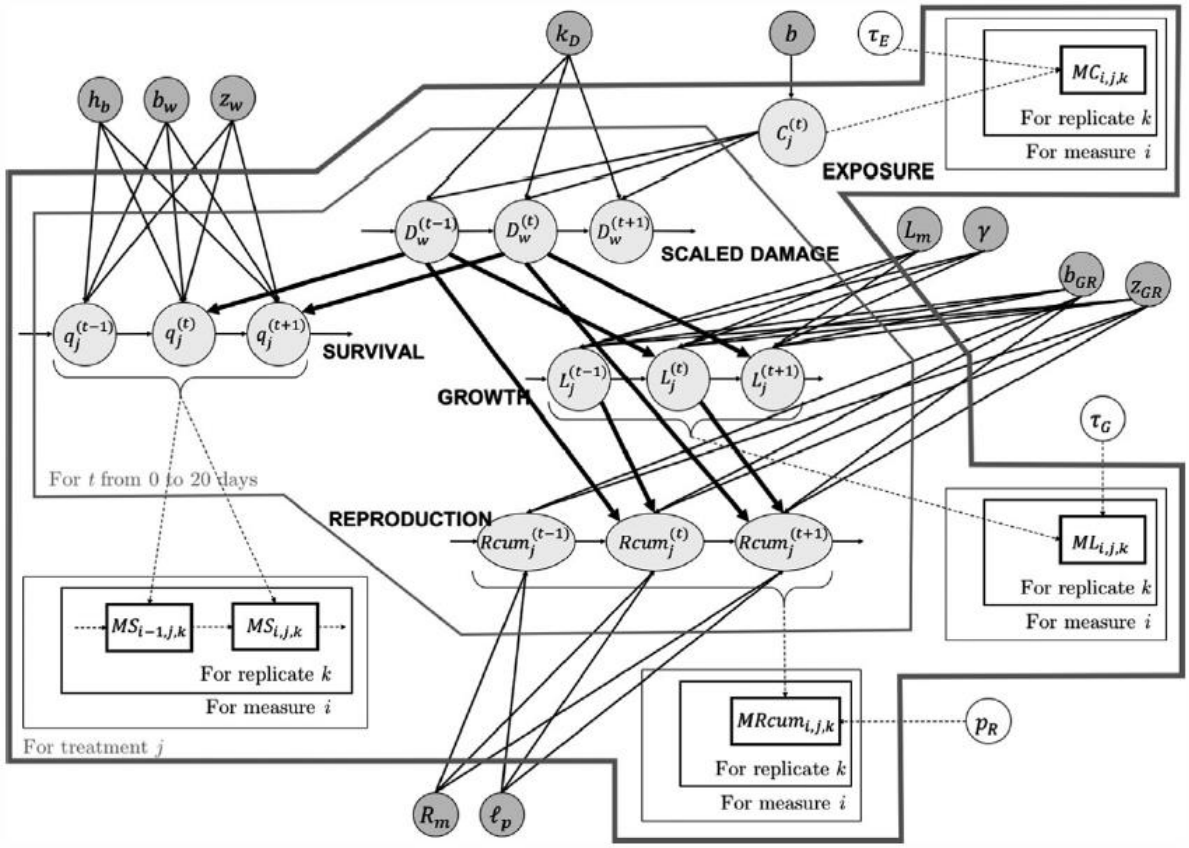

Figure 27: Directed acyclic graph of the DEBtox model used to describe time-variable cadmium effect on survival, growth and reproduction of *D. magna*. This graph is adapted from by Billoir et al. (2011). Variable q stands for the quantity dH/dt as in equation (4)

The idea of evaluation of DEBtox models as laid down in the TKTD SO consists basically of a separation of the physiological, pure DEB part of DEB models, and the TKTD or toxicity part, i.e. the link of the modelled processes with external exposure and toxicokinetics (see the figure above from the EFSA TKTD SO above as an illustration, only some of the parameters were related to toxicity effects).

The rationale for the suggestion of such separation was that experts for species physiology and DEB processes could do a review and based on this, an evaluation of the physiological DEB part of the model, which would imply also the definition of a standard parameter set for the DEB model of a certain species. Since this is a complex task that requires knowledge in physiological processes and their consideration of energy budget models, it is likely that such review could be better performed by DEB experts than by regulators in authorities. Some synergies with the existing, lively DEB modelling community was anticipated here, including possible use of the add-my-pet (AmP) database, where DEB parameters for a large number of species are stored, together with quality criteria and model code.

After the review and positive evaluation of the physiological DEB model, the task for evaluators for pesticide risk assessment would consist in the evaluation of the TKTD part of a DEBtox model, its application for regulatory risk assessment and possible adaptations of the DEB model parameters was thought to be more realistic to be done in the day-to-day business for evaluators.

In discussions after the release of the TKTD opinion, it turned out that there are some aspects on DEBtox model evaluation and application, which make it necessary to re-consider this approach. One of these aspects is related to statistical reasons. From a scientific-statistical point of view, it is considered necessary to use all DEBtox model parameters for model calibration, i.e. also the physiological model parameters. Standard physiological parameters could be used as starting values for parameter search/calibration, and deviations of the newly calibrated, physiological parameters from the standard parameters (i.e. new parameters outside of credible interval of the standard parameters) could give an indication for closer evaluation.

Another aspect is related to the fact that in the meantime the development of simplified, more targeted DEB-based models have been developed and shown. Publications for most (all?) of them is still on the way. The basic idea behind such simplified, more targeted models is to always use a model which provides appropriate complexity for the underlying risk assessment question and the choice of the species (mode details see reader on DEB-TKTD model variants by N.Sherborne).

Such simplified models would have the advantage of that the physiological DEB part of the model would probably not need an external expert review. Still, the question remains how evaluators could decide about realism and quality of any lumped parameters of simplified DEBtox models. In addition, there is a suggestion to gradually increase model complexity of the DEB-TKTD models (see reader N.Sherborne, from priDEB to priDEBkiss to comDEBkiss). Such modelling framework is a real support in a most efficient targeting of model application, but of course raises the question how long one of the concrete models would be 'simple' enough to allow evaluation by risk evaluators in agencies as routine work.

Relevance in the context of the discussion of a suite of tailor-made DEB-TKTD models or a single unified DEBtox model (the reader of T. Jager) has also the question where these models are going to be used in the regulatory risk assessment. If the intention of the DEBtox model application is alone as Tier-2 approach, simplifications will probably be acceptable, but if DEBtox models would appear also interesting for using them as building blocks in population modelling approaches, some of the simplifications which are suggested in the DEB-TKTD models reader would prohibit any further use of such targeted modelling approaches outside of (current) Tier-2 ERA.

Third aim: Identify possible use of DEBtox or DEB-TKTD applications in ERA and related scenarios.

One of the main differences between GUTS and DEBtox is the importance of time– whereas in GUTS the individuals are supposed to be static, without development outside of toxicokinetics or toxicodynamics, in DEB individuals are highly dynamic also in their physiology. In consequence, time point and duration of exposure matters, which poses a challenge on possible approaches to calculate regulatory endpoints from DEBtox models, such as e.g. the calculation of EPx values in the same way the GUTS model is used to calculate LPx or EPx values. Concerning the duration of exposure, one possibility would be to assume that exposure can theoretically always comprise the whole life span of an individual, so the development of specific models to account for short-termed periods doesn't appear very relevant. This would have implications for the model complexity and the number of parameters, and in doubt mean a considerable effort to parameterise the DEB model, despite in single cases only a single peak per scenario would be evaluated. Concerning the timing of the peak, as long as it is clear what the mode of action is, the timing of the peak in relation to the life stage of the individual can be handled by simulations. For example, in a simple approach the exposure scenario could be evaluated for the whole set of days in lifetime (or life stages) of individuals, leading to a set of simulation outcomes. From these results, the most conservative or appropriate results can be taken.

Another aspect of relevance on DEBtox models which is different from GUTS is the need to have a proper handling of starvation. Related to that, perhaps, the question of maturation as explicit submodule or at fixed size. Starvation is a natural process, which is a part of wild life, and can pose additional stress on individuals who are exposed to chemicals. In addition, if DEB models are considered as building blocks for population models, starvation plays an absolute crucial role since density dependent self-regulation of population size functions via starvation and consequent mortality of part of a population.

References

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