Peer Community In Ecology

Addressing uncertainty in Environmental Risk Assessment using mechanistic toxicological models coupled with Bayesian inference

Luis Schiesari *based on peer reviews by* ***Andreas Focks*** *and 2 anonymous reviewers*

Virgile Baudrot and Sandrine Charles (2018) Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models. bioRxiv, ver. 1, peer-reviewed and recommended by Peer Community in Ecology. 10.1101/356469

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Environmental Risk Assessment (ERA) is a strategic conceptual framework to characterize the nature and magnitude of risks, to humans and biodiversity, of the release of chemical contaminants in the environment. Several measures have been suggested to enhance the science and application of ERA, including the identification and acknowledgment of uncertainties that potentially influence the outcome of risk assessments, and the appropriate consideration of temporal scale and its linkage to assessment endpoints [1]. Baudrot & Charles [2] proposed to approach these questions by coupling toxicokinetics-toxicodynamics models, which describe the time-course of processes leading to the adverse effects of a toxicant, with Bayesian inference. TKTD models separate processes influencing an organismal internal exposure (´toxicokinetics´, i.e., the uptake, bioaccumulation, distribution, biotransformation and elimination of a toxicant) from processes leading to adverse effects and ultimately its death (´toxicodynamics´) [3]. Although species and substance specific, the mechanistic nature of TKTD models facilitates the comparison of different toxicants, species, life stages, environmental conditions and endpoints [4]. Baudrot & Charles [2] investigated the use of a Bayesian framework to assess the uncertainties surrounding the calibration of General Unified Threshold Models of Survival (a category of TKTD) with data from standard toxicity tests, and their propagation to predictions of regulatory toxicity endpoints such as *LC(x,t)* [the lethal concentration affecting any x% of the population at any given exposure duration of time t] and *MF(x,t)* [an exposure multiplication factor leading to any x% effect reduction due to the contaminant at any time t]. Once calibrated with empirical data, GUTS models were used to explore

individual survival over time, and under untested exposure conditions. Lethal concentrations displayed a strong curvilinear decline with time of exposure. For a given total amount of contaminant, pulses separated by short time intervals yielded higher mortality than pulses separated by long time intervals, as did few pulses of high amplitude when compared to multiple pulses of low amplitude. The response to a pulsed contaminant exposure was strongly influenced by contaminant depuration times. These findings highlight one important contribution of TKTD modelling in ecotoxicology: they represent just a few of the hundreds of exposure scenarios that could be mathematically explored, and that would be unfeasible or even unethical to conduct experimentally. GUTS models were also used for interpolations or extrapolations of assessment endpoints, and their marginal distributions. A case in point is the incipient lethal concentration. The responses of model organisms to contaminants in standard toxicity tests are typically assessed at fixed times of exposure (e.g. 24h or 48h in the *Daphnia magna* acute toxicity test). However, because lethal concentrations are strongly time-dependent, it has been suggested that a more meaningful endpoint would be the incipient (i.e. asymptotic) lethal concentration when time of exposure increases to infinity. The authors present a mathematical solution for calculating the marginal distribution of such incipient lethal concentration, thereby providing both more relevant information and a way of comparing experiments, compounds or species tested for different periods of time. Uncertainties were found to change drastically with time of exposure, being maximal at extreme values of x for both *LC(x,t)* and *MF(x,t)*. In practice this means that assessment endpoints estimated when the effects of the contaminant are weak (such as LC10, the contaminant concentration resulting in the mortality of 10% of the experimental population), a commonly used assessment value in ERA, are prone to be highly variable. The authors end with recommendations for improved experimental design, including (i) using assessment endpoints at intermediate values of x (e.g., LC50 instead of LC10) (ii) prolonging exposure and recording mortality over the course of the experiment (iii) experimenting one or few peaks of high amplitude close to each other when assessing pulsed exposure. Whereas these recommendations are not that different from current practices, they are based on a more coherent mechanistic grounding. Overall, this and other contributions from Charles, Baudrot and their research group contribute to turn TKTD models into a real tool for Environmental Risk Assessment. Further enhancement of ERA´s science and application could be achieved by extending the use of TKTD models to sublethal rather than lethal effects, and to chronic rather than acute exposure, as these are more controversial issues in decision-making regarding contaminated sites.

References:

[1] Dale, V. H., Biddinger, G. R., Newman, M. C., Oris, J. T., Suter, G. W., Thompson, T., ... & Chapman, P. M. (2008). Enhancing the ecological risk assessment process. Integrated environmental assessment and management, 4(3), 306-313. doi: [10.1897/IEAM_2007-066.1](https://dx.doi.org/10.1897/IEAM_2007-066.1)

[2] Baudrot, V., & Charles, S. (2018). Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models. bioRxiv, 356469, ver. 3 peer-reviewed and recommended by PCI Ecol. doi: [10.1101/356469](https://dx.doi.org/ 10.1101/356469)

[3] EFSA Panel on Plant Protection Products and their Residues (PPR), Ockleford, C., Adriaanse, P., Berny, P., Brock, T., Duquesne, S., ... & Kuhl, T. (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), e05377. doi: [10.2903/j.efsa.2018.5377](https://dx.doi.org/10.2903/j.efsa.2018.5377)

[4] Jager, T., Albert, C., Preuss, T. G., & Ashauer, R. (2011). General unified threshold model of survival-a toxicokinetic-toxicodynamic framework for ecotoxicology. Environmental science & technology, 45(7), 2529-2540. doi: [10.1021/es103092a](https://dx.doi.org/ 10.1021/es103092a)

Reviews

Evaluation round #1

DOI or URL of the preprint: https://doi.org/10.1101/356469
Version of the preprint: 1

Authors' reply, 08 November 2018

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Decision by Luis Schiesari, posted 08 November 2018

revision needed

Dear Dr. Baudrot,

Thank you for submitting your manuscript "Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models" to PCI Ecology.

I have now received three constructive reviews, which will be fowarded to you in a separate email.

All three referees and myself consider the manuscript to be relevant and meritorious. Referee 1 had only minor comments to the manuscript and thought these minor comments did not justify a revision. Referee 2, in turn, had several comments, particularly with respect to more appropriately framing the contribution of the manuscript, and to improve Abstract, Discussion and Conclusion. Referee 2 also urged the manuscript to be reviewed by an expert in TKTD models. I then invited a third reviewer (Andreas Focks, who waived anonymity). He recognized the mathematical quality of the manuscript but made several suggestions to improve the clarity of the text.

I therefore invite you to submit a revised version of your manuscript, accompanied by a response letter describing how the referees comments were addressed.

Sincerely, Luis Schiesari Recommender, Peer Community in Ecology

Reviewed by anonymous reviewer 1, 24 July 2018

This manuscript explores the use of TKTD models to reduce uncertainties in ERA. The topic is highly relevant and timely the more since the use of such models have (as the authors also indicate) been proposed for use by Legislative bodies such as EFSA in EU. The paper is very well written and besides a great overview of the state of the art, the case studies presented and discussed in the paper provide clear examples of the pros and cons of the methodology. My only (very minor) comment is that the paper is rather long, which is at least partly due that some text in the results section already discuss findings (e.g. P 12 Lns 260-264). In addition, names of active substances should be written in small (not capital) letters (e.g. P 9 Lns 236/237). Authors also often focus on the use of the method for setting EQS (e.g. P 17 Ln 372), which implies that it would be especially useful for retrospective ERA. Although PNEC (which is not an EQS and especially used in prospective ERA) is mentioned, maybe indicating in the Introduction section that it can be used in both prospective and retrospective ERA would give more justice to this very interesting work. These comments, however, do in my opinion not justify recommending revision and I would therefore highly recommend this paper for colleagues working in this area and ERA in general.

Reviewed by anonymous reviewer 2, 30 July 2018

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Reviewed by **Andreas Focks**, 09 September 2018

Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models The manuscript presents analyses of TKTD models for survival, i.e. the GUTS models, which investigate properties of these models in the light of regulatory risk assessment. Based on an earlier published and analysed example data set, the authors derive analytical mathematical solutions of the reduced GUTS models under constant external exposure, and use these solutions in combination with the Bayesian inference method for model calibration and analyses of the propagation of parameter uncertainty to model predictions. Based on the derived mathematical framework, the authors analyse the uncertainty in model predictions for some scenarios, e.g. constant vs time-variable exposure, as well as properties of LC estimates over time, or as a function of the effect percentage. Further on, they test the effects of different time-variable exposure patterns on the model predictions. The manuscript shows a very good mathematical quality, and interesting analyses, which are relevant for the application of TKTD models of the GUTS type for the evaluation of toxicity tests. The presented work is highly relevant and can be clearly recommended for publication in PCI ecology. Alone, the language is not fit for publication, and there are some formulations in the text which need to be rephrased in order to clarify the sentences or to avoid misunderstandings. In my review, I suggest some reformulations, and I corrected also some language issues, but I strongly recommend to let the manuscript be edited by a native speaker/expert.

Detailed comments in the pdf.

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