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RECOMMENDATION

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

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A recommendation of
Baudrot V and Charles S. Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models. *bioRxiv* 356469, ver. 3 peer-reviewed and recommended by *PCI Ecol* (2018). DOI: 10.1101/356469

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 [2].

Baudrot and Charles [1] 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') [4]. Although species and substance specific, the mechanistic nature of TKTD models facilitates the comparison of different toxicants, species, life stages, environmental conditions and endpoints [3].

Baudrot and Charles [1] 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 percent of the population at any given exposure duration of time t] and *MF(x,t)* [an exposure multiplication factor leading to any x percent 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 percent 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 con-

tribute 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] Baudrot V and Charles S. Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models. *bioRxiv* 356469, ver. 3 peer-reviewed and recommended by *PCI Ecol* (2018). DOI: 10.1101/356469.

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Appendix

Reviews by Andreas Focks and two anonymous reviewers, DOI: 10.24072/pci.ecology.100007