Session: Effect Modelling for Regulatory Risk Assessment: Current Applications and Future Directions (I)
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A roadmap for the use of TKTD models in ERA of pesticides

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1. Introduction

Current lower-tier (Tier 1) risk assessments for pesticide active substances and Plant Protection Products (PPPs) in surface waters [1] rely on the quantification of treatment-related responses from protocol tests, where exposure is continuous. However, under realistic field situations, concentrations vary in time, sometimes by orders of magnitude in a matter of hours [2]. When a low risk cannot be demonstrated with this conservative Tier-1 data, one possibility is to address the mismatch between the more or less constant exposure regime used in standard ecotoxicity tests and the time-variable concentrations in the real environment [3].
Several ways to tackle this issue have been proposed in the EU aquatic risk assessment scheme [1]. Among those, effect modelling offers a valid alternative for dealing with time-variable exposure. Particularly, toxicokinetic-toxicodynamic (TKTD) models can be used to predict individual-level effects under untested time-variable exposure conditions. These models, despite presenting different levels of complexity, involve parameters having a rather clear physical or biological meaning [4].
While TKTD models have been widely used for several years for research purposes, their application in regulatory risk assessment has been very limited. The main reason for this is likely the lack of clear, harmonised guidance about how risk assessors should evaluate and interpret these models and their application. In order to overcome this issue, and following a request from EFSA, the Panel on Plant Protection Products and their Residues (PPR) developed a Scientific Opinion (SO) [5] on the state of the art of TKTD models and their use in prospective environmental risk assessment (ERA) for pesticides and aquatic organisms.
In the SO, three different types of TKTD models are described: (i) the 'General Unified Threshold models of Survival' (GUTS), (ii) models based on the Dynamic Energy Budget theory (DEBtox models), and (iii) models for primary producers. For each of those, the current state regarding their applicability in the risk assessment of pesticides was discussed, and targeted criteria were given about how these models should be evaluated. The aim of this platform will be to present the assessment strategy suggested in the opinion, focussing specifically on GUTS models since this type of models has been considered ready to be used for risk assessment.

2. Model evaluation

In order to follow the recommendations given by the EFSA SO on good modelling practice [6], ten different evaluation areas have been identified and organised in checklists for each TKTD model type. For GUTS, due to the standardised nature of such models, some of these areas (e.g. evaluation of the formal model, evaluation of the conceptual model, evaluation of the environmental scenarios, etc.) have been considered addressed once for all in the remit of the SO, so that they should not be re-assessed for any new application. On the contrary, other areas need to be carefully considered in the context of any substance-specific assessment. Among those, particular attention should be paid to the parameter estimation (model calibration), to the evaluation of the sensitivity and uncertainty, and to the evaluation of the model by comparison with independent measurements (model validation).

2.1. Model calibration

The SO specifies that any GUTS model should be calibrated for each specific combination of toxic substance and exposed organism. Among other recommendations, the SO gives guidance about the experimental data to be used as input for the calibration. In particular, the design of the toxicity test used for calibration should present a minimum number of time points and should cover an appropriate extent of the full dose-response relationship. In addition, other recommendations concern the reporting of the uncertainty around the parameter estimations, the assessment of the goodness-of-fit (e.g. visual match of fitting plots,

posterior-predictive checks, etc.), and the way background/control mortality should be handled in the calibration phase.

2.2. Sensitivity and uncertainty

The SO recognised that a sound sensitivity analysis is pivotal as it quantifies the influence of parameters on the model outputs. In this respect, the range of parameter variation in the sensitivity analysis should be justified by an analysis of the expected variation of model parameters. The SO already proposed a sensitivity analysis of the reduced versions of GUTS (i.e. direct link between external concentrations and scaled damage). Hence, for applications of these model versions, no further sensitivity analysis is requested.

A proper uncertainty analysis should make sure that the uncertainty around the model parameter estimation is propagated to the model output. Hence, model outputs should be reported including confidence/credible intervals.

2.3. Model validation

One of the most important steps of the modelling cycle for risk assessment purposes is the evaluation of the model by comparison with independent measurements (model validation). For GUTS, experimental validation data, which were not used for model calibration, can be used to test the model performance for predictions of mortality/immobility under exposure profiles. The performance of the model is evaluated by comparing relevant model outputs with experimental measurements.

The SO gives recommendations about the experimental test design to be used for validation. In particular, it defines: (i) a minimum number of measurements in time; (ii) a minimum number of exposure profiles in terms of shape (i.e. number of exposure pulses and interval between them) and magnitude (i.e. peak concentrations); (iii) the extent of the range of total effect to be achieved. In addition, the SO gives recommendations for the methods and the metrics to be used for assessing the predictive capacity of the model, when predictions are compared to the validation data.

3. Implication for testing

A proper application of TKTD models for regulatory risk assessment relies heavily on experimental data of good quality. Such experimental data are needed in two different phases of the modelling cycle. For calibrating GUTS, testing under static exposure is likely to be sufficient, in which case additional data to those listed in the standard data requirement may not be needed, if the calibration follows the recommendations given in 2.1. On the contrary, validation data need ad-hoc experimental design, in order to meet the recommendations of the SO. It should be pointed out that testing under time-variable concentrations is already proposed as an option for refining the risk to aquatic organisms since several years [1]. The use of the TKTD, however, should help the interpretation of the results of these tests, and will make it possible to extrapolate the results to any kind of untested exposure pattern.

4. References

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