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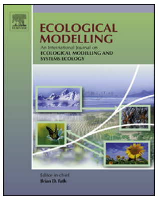

Incorporating toxicokinetics into an individual-based model for more realistic pesticide exposure estimates: A case study of the wood mouse

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ABSTRACT

The potential risk of agricultural pesticides to mammals typically depends on internal concentrations within individuals, and these are determined by the amount ingested and by absorption, distribution, metabolism, and excretion (ADME). Pesticide residues ingested depend, amongst other things, on individual spatial choices which determine how much and when feeding sites and areas of pesticide application overlap, and can be calculated using individual-based models (IBMs). Internal concentrations can be calculated using toxicokinetic (TK) models, which are quantitative representations of ADME processes. Here we provide a population model for the wood mouse (*Apodemus sylvaticus*) in which TK submodels were incorporated into an IBM representation of individuals making choices about where to feed. This allows us to estimate the contribution of individual spatial choice and TK processes to risk. We compared the risk predicted by four IBMs: (i) "AllExposed-NonTK": assuming no spatial choice so all mice have 100% exposure, no TK, (ii) "AllExposed-TK": identical to (i) except that the TK processes are included where individuals vary because they have different temporal patterns of ingestion in the IBM, (iii) "Spatial-NonTK": individual spatial choice, no TK, and (iv) "Spatial-TK": individual spatial choice and with TK. The TK parameters for hypothetical pesticides used in this study were selected such that a conventional risk assessment would fail. Exposures were standardised using risk quotients (RQ; exposure divided by LD_{50} or LC_{50}). We found that for the exposed sub-population including either spatial choice or TK reduced the RQ by 37–85%, and for the total population the reduction was 37–94%. However spatial choice and TK together had little further effect in reducing RQ. The reasons for this are that when the proportion of time spent in treated crop (PT) approaches 1, TK processes dominate and spatial choice has very little effect, and conversely if PT is small spatial choice dominates and TK makes little contribution to exposure reduction. The latter situation means that a short time spent in the pesticide-treated field mimics exposure from a small gavage dose, but TK only makes a substantial difference when the dose was consumed over a longer period. We concluded that a combined TK-IBM is most likely to bring added value to the risk assessment process when the temporal pattern of feeding, time spent in exposed area and TK parameters are at an intermediate level; for instance wood mice in foliar spray scenarios spending more time in crop fields because of better plant cover.

1. Introduction

The exposure of small mammals to agricultural pesticides is to a large extent driven by the spatial overlap between feeding areas and pesticide application. Thus, the dose small mammals ingest is a result of the concentration of pesticide residues on different types of food items and how large a proportion of their diet is obtained from treated areas (EFSA, 2009). However, it is generally the internal concentration in the body (body burden) or target tissue, that drives the toxicological effects and apart from ingested dose this also depends on absorption, distribution, metabolism,

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and excretion (ADME) processes, as well as on the temporal pattern of feeding. The spatially-specific toxicant ingestion patterns and the temporal-specific ADME processes are individually quite well understood but no attempt has been made to integrate the two types of processes to provide a single assessment of risk.

In conventional risk assessments, the overlap between feeding sites and application area is typically dealt with by radio-tracking studies to estimate the proportion of time spent in the treated crop (PT) (EFSA, 2009). However, PT is not a constant but depends on both landscape context and the ecology of the species. These relationships are difficult to study in the field and so Individual-Based Models (IBMs; Grimm and Railsback, 2005; Railsback and Grimm, 2012) have been used to simulate the spatial choice of animals and predict population-level impact of pesticides (Topping et al., 2005; Wang and Grimm, 2007; Ashauer and Escher, 2010). These models calculate where and when each individual feeds, and how much it eats and so calculate the dose of pesticide ingested. However the risk to the animal depends not only on the total amount but also on the temporal pattern of ingestion, because the proximate cause of toxicity is internal concentration and this is affected by excretion and metabolism as well as by ingestion. For instance, if an animal forages over a large area, feeding will typically take longer than if all the necessary food can be found in a small area. The resulting internal concentration may be lower in the former case due to effective elimination between foraging occasions. Therefore, the two types of models have the potential to complement each other and provide an improved estimate of exposure: TK processes can complement IBM because exposure depends not only on how much toxicant is eaten, but also on how much of the eaten dose is absorbed and eliminated. IBMs can complement TK models because in the natural environment, the ingestion of toxicant very rarely follows a constant rate or gavage dose as assumed in standard chronic or acute tests for mammals, but is rather strongly affected by the spatio-temporal pattern of feeding.

In pesticide risk assessment, internal concentration has been modelled based on ADME processes using toxicokinetic (TK) models (aka "body-burden models") (Jager et al., 2011) and the temporal pattern of feeding has been shown to be important for terrestrial vertebrates (Bednarska et al., 2013). The simplest TK model has a single compartment and first-order kinetics. Despite its simplicity, the model generally captures the kinetics of the concentration of pesticide in the whole body well for those pesticides which reach equilibrium concentrations within different tissues in the order of hours and for which concentration in target tissue(s) is highly correlated with concentration in other tissues. Key parameters in the TK model are absorption (k_a) and elimination (k_e) rate constants, which respectively reflect how quickly toxicant goes into the body and how quickly it is eventually eliminated from the organism. It has been shown that a one-compartment model can be used to test how different feeding patterns (e.g. constant fast feeding, constant slow feeding or feeding with breaks) may influence the peak internal concentration of pesticide in the body (Bednarska et al., 2013). For many rapidly excreted active substances, acute effects are usually associated with peak internal concentration (Barton et al., 2006), though this needs to be confirmed in each case.

There is hence need to develop IBMs in which each individual is equipped with TK properties and processes, an area little explored until now (but see Loos et al., 2010; Engelman et al., 2012). Here, we combine a simple TK model (Bednarska et al., 2013) with an IBM of the wood mouse (*Apodemus sylvaticus*) (Liu et al., 2013) so we can predict exposure both at the organism and population level. This is necessary for ecological risk assessments, where the protection goal is no adverse impacts at the population level, and for mammals also no visible mortality (EFSA, 2010). In an agricultural habitat, the wood mouse is a focal species potentially exposed to pesticides through eating an omnivorous diet comprising of seeds, some of which may be treated (i.e. seeds coated with pesticide). We address the following questions: (1) How much may TK and IBM (spatial choice) separately modify conventional risk assessment? (2) How much does the combination of TK processes and realistic temporal patterns of feeding and spatial choice together change the predicted risk? (3) How do TK and spatial choice interact and affect the exposure estimates?

2. Methods

2.1. Model description

The model description follows the ODD (Overview, Design concepts, Details) protocol for describing individual-based models (Grimm et al., 2006, 2010).

2.1.1. Purpose and general overview

The purpose of the model is to explore the contribution and interaction of both spatial choice and TK processes to the risk to wood mouse population in a seed treatment scenario.

The model we use in this study was derived from an existing IBM here called the "base model" (Liu et al., 2013). The base model represents the full life cycle of the female wood mouse, with special focus on the habitat choice for foraging and nesting sites. Mice decide where to go based on the quality of plant cover. Population dynamics and proportion of different habitats in mouse feeding sites can be tracked. For our current model, we kept most aspects of the base model but made changes necessary for the purposes of the present study. These were:

(1) mouse habitat choice now includes newly drilled field for treated crop seeds;
(2) inclusion of TK (absorption and elimination) processes for the calculation of internal concentration of pesticide;
(3) pesticide-induced mortality predicted by individual dose- (or concentration-) response curves.

The model is implemented in NetLogo 4.1 (Wilensky, 1999). Both the NetLogo model and the model documentation (here in the form of a TRACE document, i.e. transparent and comprehensive ecological modelling documentation; Schmolke et al., 2010) are available in the Supplementary Materials. All simulations were run with 20 replicates (for justification see TRACE).

2.1.2. Entities, state variables, and scales

The entities and their state variables are as in the base model (Liu et al., 2013), but with the following changes. Variables are shown in italics.

(1) Habitat and ingestion: in the current model, the landscape consists of one ten-hectare winter wheat field (instead of four different crop fields in the base model), so crop rotation is not considered. The wheat field is surrounded by 5-m wide hedgerows. The total size of the landscape is 10.4 ha, which is represented as 101 × 41 square patches, with torus setting to avoid edge effect. For patches there are only two options for *habitat type*: hedgerow or winter wheat (this takes into consideration crop growth through to harvest, stubble after harvest and then fallow before sowing). *Time and farming activities* are listed in Table 1. *Plant cover* in the current model is given as % ground cover (Table 1) instead of "good" or "bad" in the base model. Mice have a certain *probability of eating wheat seeds* in newly drilled field. Mice choose between the two types of habitat (hedgerows and wheat field) based on *plant cover* and *probability of eating wheat seeds*. The *body weight* of individual