1.7 The advantage of a toxicokinetic model of the honey bee colony in the context of the risk assessment of plant protection products

Kerstin Hörig[1], Christian Maus[2], Alexander Nikolakis[2], Hans-Toni Ratte[3], Martina Roß-Nickoll[1], Walter Schmitt[4], Thomas G. Preuss[1,2]

[1]Institute for Environmental Research, RWTH Aachen University, Aachen, Germany
[2]Bayer CropScience AG, Monheim am Rhein, Germany
[3]gaiac - Research Institute for Ecosystem Analysis and Assessment, Aachen, Germany
[4]Bayer Healthcare AG, Wuppertal, Germany

Corresponding author:

Kerstin Hörig, kerstin.hoerig@bio5.rwth-aachen.de, Phone +49 (0) 241 / 80-23693
Institute for Environmental Research, Worringerweg 1, 52074 Aachen, Germany

Abstract

Within the current discussions about risk assessment of plant protection products regarding honey bees, one of the most important aspects is how to link pesticide exposure on field and landscape scale to potential effects within the colony. A dynamic toxicokinetic model may help to improve the evaluation of dose rates individuals are exposed to through various compartments of the colony, which may result from the application of plant protection products in the field. In addition, it may help to interpret the significance of ecotoxicological test results, especially from lower-tier studies, in the risk assessment and help to refine the exposure assessment and risk evaluation. Linking it to a realistic population model and a landscape-based foraging model would give an improved insight into the dynamics in a honey bee colony under exposure of plant protection products

Keywords: Modelling, Toxicokinetics, Risk Assessment, Exposure

1. Introduction

1.1 Regulatory background

In 2012 the European Food Safety Authority (EFSA) published a scientific opinion on the science behind the development of a risk assessment of PPPs on bees (*Apis mellifera, Bombus* spp. and solitary bees) as an answer to a request from the European Commission.[1] In this paper, the importance of the linkage of exposure and effects is stressed. In 2013 this scientific opinion was followed by a Draft Guidance on the risk assessment of PPPs on bees in order to "provide guidance for notifiers and authorities in the context of the review of PPPs and their active substances under Regulation (EC) 1107/2009".[2] This draft guidance document demands several tests to determine the effects of PPPs on honey bees, bumble bees, and solitary bees of which only a part are conductible with a validated test guideline, e.g. by OECD.[3,4] For many of the proposed risk assessment procedures, a key issue is the determination of the exposure of bees to PPPs on colony level. A modelling approach may help to close knowledge gaps in this context and to support the risk assessment with scientifically robust information on exposure, which may otherwise be very complex to determine experimentally.

1.2 Modelling in the regulatory context

Models may be used as valuable tools to address ecological and ecotoxicological questions that may be raised in the risk assessment of PPPs.[5] One reason for the use of models in the risk assessment of PPPs is the reduction of animals that shall be used in tests. The Regulation (EC) No 1107/2009 stresses the promotion of non-animal test methods and alternative risk assessment approaches.[6] Furthermore, a model may help extrapolating from laboratory to field conditions under consideration of landscape effects. A particularly important potential use of models in risk assessment of PPPs may be the refinement of the exposure assessment.[5]

Models of special interest for the risk assessment of PPPs are

1. models that may be used for the quantification of specific protection goals and the setting of trigger values

2. models that refine the effect or exposure assessment

3. models that help with the interpretation of higher tier study data

4. models that complement and integrate information from higher tier studies

5. models that may extrapolate to scenarios not covered by higher-tier testing or may be used in situations where field studies are not feasible.[5]

In the following a selection of existing models that describe aspects of the honey bee colony with interest for the ecotoxicological risk assessment are outlined. The colony model BEEHAVE [7] predicts the colony dynamics of the honey bee and the dynamics of the resources within the hive, the population dynamics of the *Varroa* mite, an important parasite of the honey bee, and the epidemiology of *Varroa*-transmitted viruses. The model allows foragers in an agent-based foraging submodel to collect food which is presented from a representation of a spatially explicit landscape.[7] In contrast to other published honey bee models it combines in-hive dynamics and pathology with foraging dynamics.[8] Its value for the risk assessment of PPPs for honey bees comprises the potential for a quantification of specific protection goals and trigger values for the consideration of 'risk mitigation measures, refined exposure assessments and/or higher tier effects studies',[2] its usefulness to interpret higher tier study data, and its potential to be used for the extrapolation to situations not covered by studies.

A model that investigates how the forager bee death rate influences colony strength was used by the EFSA to translate hypothetical effects on colony size into a corresponding forager mortality in order to derive trigger values for the risk assessment.[2,9] However, this model was not developed with a regulatory purpose and is not integrating in-hive dynamics, and the effects of pathogens and foraging dynamics as for example the BEEHAVE model does.

A toxicokinetic model that describes the intake of PPPs into the colony, their distribution within the colony, and their elimination from the colony could be of potential use for the refinement of the exposure assessment. An existing model has been applied successfully to only a single exemplary case and describes only the fate of τ-fluvalinate.[10] For further validation more parameters such as the compartment capacities and the exchange parameters for the substances of interest would have to be experimentally investigated. As a better validated model of the toxicokinetics of substances in the honey bee colony has a value either as a prognostic tool for the deliberate application of pesticides to the hive (e.g., acaricides) or the inadvertent contamination of the colony (by PPPs, for instance),[11] the aim of this work is the design of a model that shall be able to describe the fate of substances within the honey bee colony – from the different potential routes of exposure to its terminus. For this, the dynamics of the honey bee colony shall be taken into consideration. A proposed model is potentially linkable to a) a model that predicts the dynamics of the honey bee colony and resources within the colony as well as b) a model that predicts the transport of resources to the colony and their potential contamination by PPPs.

2. The model approach

The most important resources for a potential intake of PPPs by the colony are nectar and pollen.[1] The processes that connect the different compartments in the colony are associated with female worker bees, which are the most important factor for substance distribution within the colony.[12] Figure 1 shows the conceptual model that takes the most important compartments and processes within the honey bee colony into account in order to predict the concentrations of PPPs in honey, bee bread, and wax, as well as the exposure concentrations of the different castes and age-classes of honey bees. The in-hive population and forager dynamics as well as the PPP residue levels in nectar and pollen might act as potential links to other models that predict further aspects of the honey bee colony. The contamination of nectar and pollen with PPPs may be derived from a

landscape-based foraging model; the in-hive population and forager dynamics may be obtained from population models. Important outcomes of a toxicokinetic model of the honey bee colony will be a) the distribution of PPPs within the resources that are brought into the colony via forager and food processor bees, b) the distribution of PPPs between wax and the matrices contained in wax compartments (honey, bee bread, brood), and c) the distribution of PPPs from the honey and the bee bread as energy and protein sources for the nurse bees into the jelly they produce.
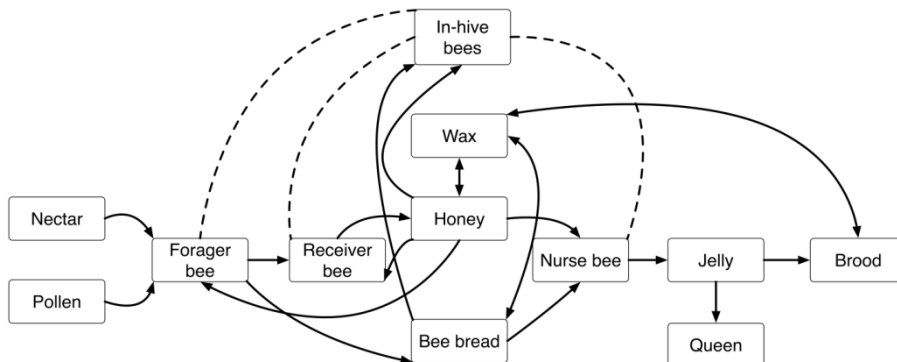

Figure 1 The toxicokinetic modelling approach – The different compartments in the honey bee colony are connected through processes that are carried mostly by the female worker bees.

3. Discussion

Models may provide the knowhow to address the complexity of a honey bee colony to the degree that is needed to link ecotoxicological endpoints to effects on the colony fitness on different levels. They may help to answer the question whether adverse effects that are observed in experiments in the laboratory, and/or on the level of individual bees, may indicate a risk to honey bee colonies under realistic conditions in agricultural landscapes and beekeeping practice. One possible level of modelling is the simulation of the toxicokinetic behavior of plant protection products in the honey bee colony. The complex toxicokinetically relevant processes in the colony can be addressed with a dynamical modelling approach. This approach may help to interpret the results of lower-tier studies, which are indicative of intrinsic effect potentials rather than about potential risks, in the context of realistic field scenarios, including the consideration of realistic exposure and field application rates of plant protection products. Simulating the toxicokinetics of plant protection products within the bee hive may provide knowledge of realistic worst case scenarios regarding the amount of plant protection products that reach the bees. A model that is able to predict exposure and effect of different substances to honey bee colonies is an asset for the risk assessment as validated guidelines for this kind of approaches are still missing and as higher tier studies for honey bees to directly investigate the effects of pesticide application to the honey bee colony are complex and require substantial efforts in terms of replication.[2] In order to derive a holistic prediction of the exposure of and effects to honey bee colonies, a combination of five different model approaches (a foraging model, a landscape model, a population model, a toxicodynamic model, and a toxicokinetic model) may be a suitable solution (Figure 2). Linking a toxicokinetic model to studies that focus on forager behavior (e.g. BEEHAVE[7]) within a realistically modelled landscape (a landscape module for BEEHAVE is under preparation to be published[7]) and effects to forager bees (e.g. GUTS[13]) may help to predict the amount of a given substance that actually reaches the hive and would entail the potential of in-hive exposure of the colony. A consideration of potential effects of substances in the nectar and pollen loads on the forager bees may be necessary. A model that describes the toxicokinetics within the hive may predict exposure concentrations of the different castes and age classes of the honey bees in the colony from the known substance amounts that enter the hive. A population model (e.g. BEEHAVE[7]) that is taking

effects into account would be able to predict the population dynamics under the influence of the identified exposure concentrations. However, a change in population dynamics that is identified by the population model might again influence the kinetics of the PPP as calculated by the toxicokinetic model. And again, the distribution of the PPP that is calculated by the toxicokinetic model may influence the outcome of the forager model, as substances may also be transported from the interior of the hive to the foragers at the periphery and on the outside of the hive. A holistic model would have to be a closely linked 'supermodel' (Figure 2) to fulfil the demands for predictions of the dynamics of the bee colony as a 'superorganism'[14]. The model development needs to aim at developing a model that can be more easily validated with experimental data than existing models.

4. Conclusion

A toxicokinetic model may help to interpret the significance of ecotoxicological test results, especially from lower-tier studies, in the risk assessment and help to refine the exposure assessment and risk evaluation. Linking it to a range of realistic models would give an improved insight into the dynamics in a honey bee colony under exposure to plant protection products.
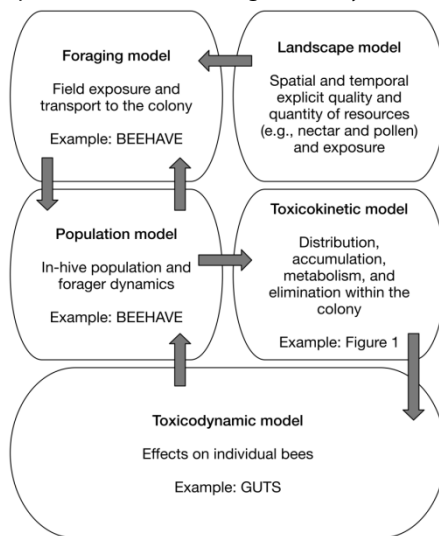
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Figure 2 The proposed honey bee 'supermodel' – A combination of a foraging model, a landscape model, a population model[7], a toxicodynamic model[13], and a toxicokinetic model (Figure 1) may give a holistic picture of the honey bee colony that is potentially exposed to pesticides in the field. The five different models would have to be closely linked, as the outcomes of each may strongly influence variables of the other models.

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