Toxicokinetics model for an insecticide in rats: implications for higher-tier risk assessment

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Introduction

The current risk assessment for mammals is based on external exposure measurements (EFSA Journal 2009, 7(12), 1438). Exposure to a chemical does not mean, however, that all of the dose will be bioavailable. Bioavailability i.e., fraction of dose that reaches the systemic circulation or is made available at the site of physiological activity (F), and toxicokinetics strongly influence the accumulated dose of a toxicant, and it is its internal concentration which makes an effect. Internal concentration is the net result of absorption, distribution, metabolism and excretion (ADME), and the toxicokinetic (TK) model is a mathematical description of these processes. We used data for an insecticide. The toxicokinetic model was parameterised using absorption, tissue distribution and excretion from a rat study with ^{14}C-labelled material. The number of compartments (tissues) in the model and the complexity of the processes of absorption and elimination were also investigated using these data. Different feeding rate scenarios were taken into account in the model because they may influence the concentration of chemical in the body and the risk for animals living in natural environments.

Methods

Fitting one-compartment model to the data

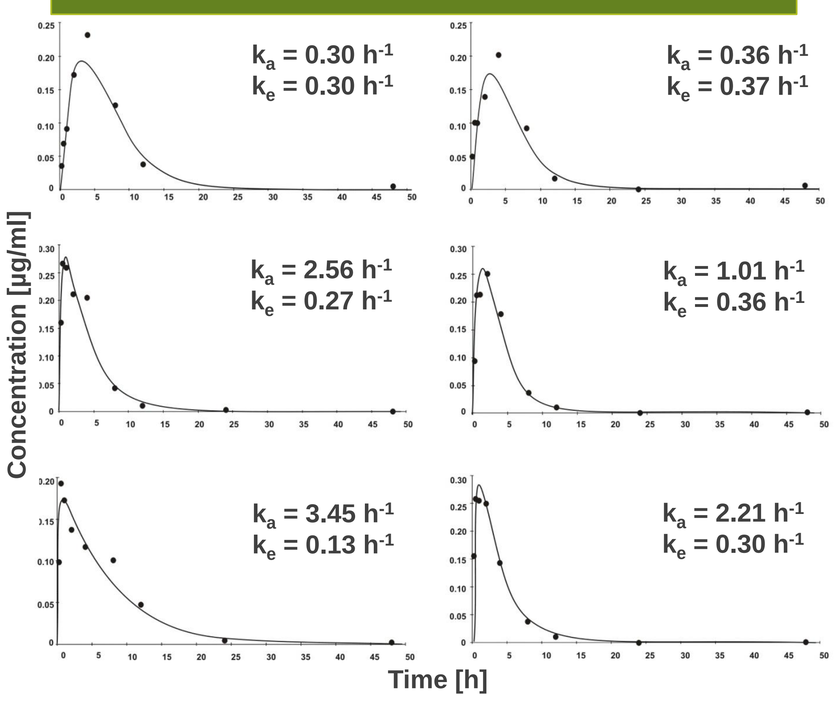

Figure 1. The concentration of an insecticide in blood of three male rats administered 0.5 mg kg^{-1} bw [Thiazol-2-^{14}C] (left-hand column) or [Oxadiazin-4-^{14}C] (right-hand column). Lines: one-compartment models fitted to the experimental data (Marquardt method).

Kinetics parameters estimated from rat study based on radiolabeled test substance

Parameters	Intravenous exposure		Oral exposure							
	[Thiazol-2-^{14}C] 0.5 mg kg^{-1} bw		[Thiazol-2-^{14}C] 0.5 mg kg^{-1} bw		[Oxadiazin-4-^{14}C] 0.5 mg kg^{-1} bw		[Thiazol-2-^{14}C] 100 mg kg^{-1} bw		[Oxadiazin-4-^{14}C] 100 mg kg^{-1} bw	
	male	female	male	female	male	female	male	female	male	female
k_a [h^{-1}]	-	-	2.1±1.62	2.3±1.93	2.2	3.2±0.29	0.78±0.32	1.6±0.71	1.3	2.00±1.37
k_e [h^{-1}]	0.26±0.02	0.4	0.23±0.09	0.23±0.13	0.34±0.034	0.25±0.0	0.28±0.12	0.18±0.06	0.25±0.11	0.19±0.06
AUC [h ug^{-1} ml^{-1}]	2.30±0.19	1.63±0.38	1.49±0.15	1.56±0.53	1.30±0.015	1.03±0.13	342±80	278±59	359±50	294±24
F	-	-	0.61±0.09	0.94±0.27	0.75±0.12	0.63±0.08	0.84±0.21	0.94±0.22	0.80±0.11	0.96±0.11

Model implementation

A one-compartment first-order model gave the best fit to the data regardless of dose, sex or exposure route. The residues in different tissues were highly correlated with each other ($r \geq 0.9$, $p \leq 0.0004$) which suggest that the insecticide is rapidly perfused throughout the body. Therefore, all tissues and blood were treated as one compartment and the gastro-intestinal tract as a second, the content of which is not strictly 'in' the organism:

$$\Delta C_{gut} = I - k_{out} C_{gut} - k_a C_{gut}$$

$$\Delta C_{\text{int}} = k_a C_{gut} F - k_e C_{\text{int}}$$

ΔC	change in the gut $_{gut}$ or internal $_{int}$ concentration of pesticide in given time interval, here one minute
I	intake rate [mg a.i. kg^{-1} bw min^{-1}]
F	bioavailability, here F =1
k_{out}	the rate of excretion of toxicant not absorbed into the system from the gut [min^{-1}], here k_{out} =0
k_a	the rate of toxicant absorption from the gut into the system [min^{-1}]
k_e	the rate of toxicant elimination from the system [min^{-1}]

The body burden model equations were implemented in the spreadsheet and after verification (Figure 2) the model was applied to a variety of exposure scenarios (Figure 3).

Results

Model verification

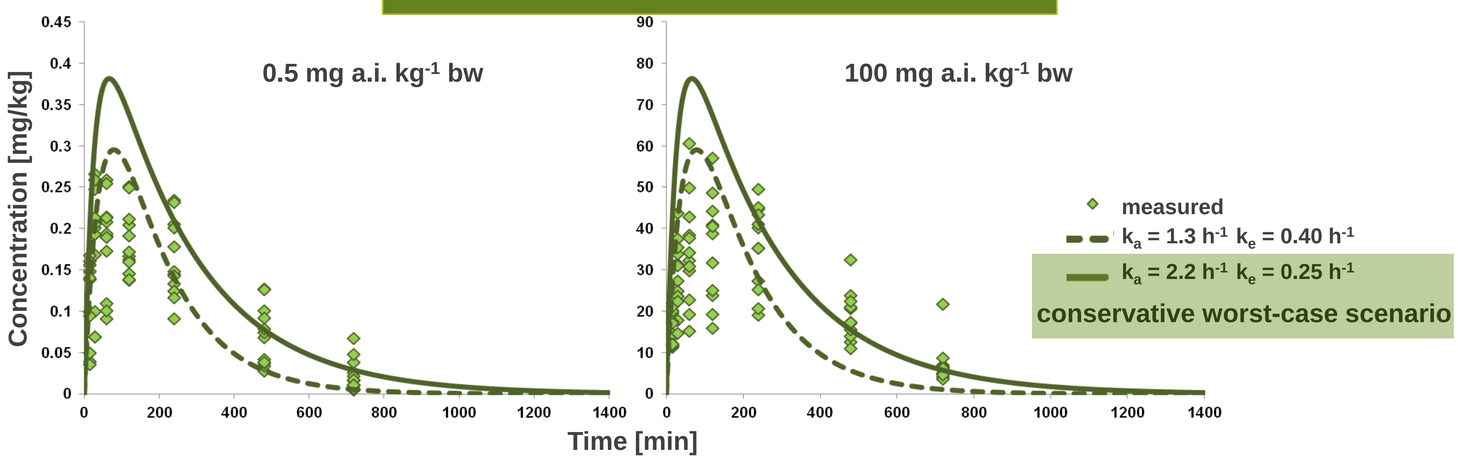

Figure 2. The concentration of an insecticide in blood of rats (points) after administration 0.5 or 100 mg a.i. kg^{-1} bw and model simulations (lines) for two extreme combinations of absorption and elimination rate constants.

Simulations of different exposure scenarios

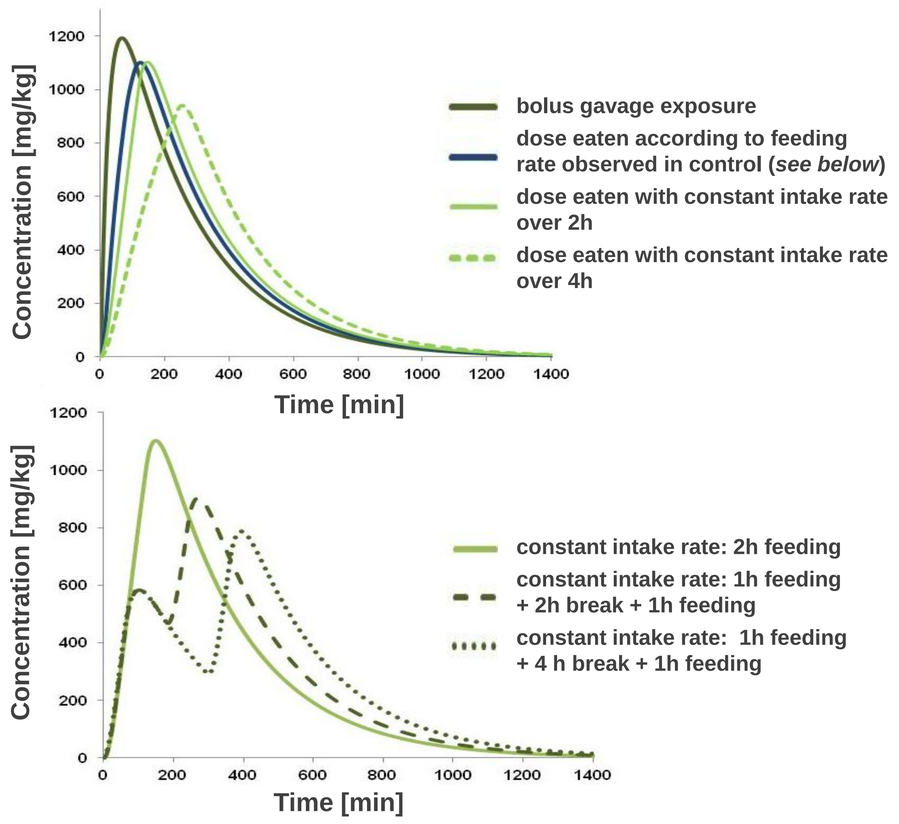

Figure 3. The concentration of an insecticide in the body when the same dose is eaten according to different feeding patterns; control feeding rate from an experiment in which rats were trained to eat all daily required dose over 2h: feeding rate decrease over time as an animal becomes satiated. All simulations for k_a = 2.2 h^{-1} and k_e = 0.25 h^{-1}.

Conclusions

The model is realistically worst-case, i.e., it captures the overall pattern, but over predicts peak internal concentrations. It shows the importance of kinetics and feeding pattern in risk assessment: the slower animals eat the lower internal maximum concentrations are reached. Feeding pattern may influence the internal concentration of pesticides, especially if there are breaks of low/no feeding activity after short feeding bouts.

Integration of ADME study and timescale of exposure is a promising approach which can improve higher-tier risk assessment.

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