# Toxicokinetics modelling in Ecotoxicology and Ecological Risk Assessment

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# Content

- The principle challenge in ecotoxicology and current risk assessment
- TK model: *what, why and how*?
- What do regulators say about TK?
- Case study: pros and cons of using body burden model in bird and mammal risk assessment


**“Applying toxicokinetics modelling to wildlife risk assessment for pesticides”**

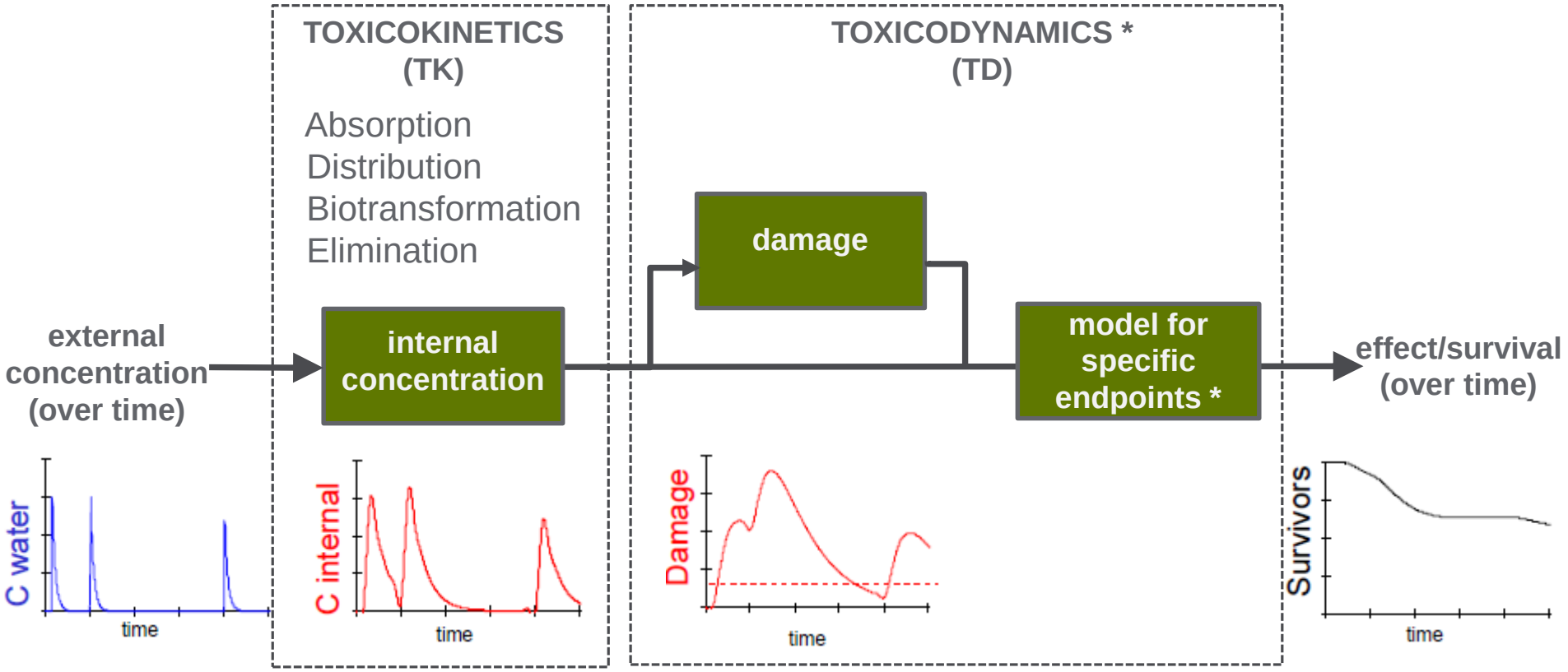
# Background

- How to accurately characterize the risk of chemicals to a diversity of species with different behaviours and sensitivities from a limited amount of information?

- The current risk assessment
  - Based on external exposure measurements
  - Do not represent field exposure

- TK model
  - Absorption, Distribution, Metabolism, Excretion (ADME)

# TK (and TD) concept




* For more details see: Jager, T., Albert, C., Preuss T. G., Ashauer, R. (2011). General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology. Environmental Science & Technology 45: 2529-2540.



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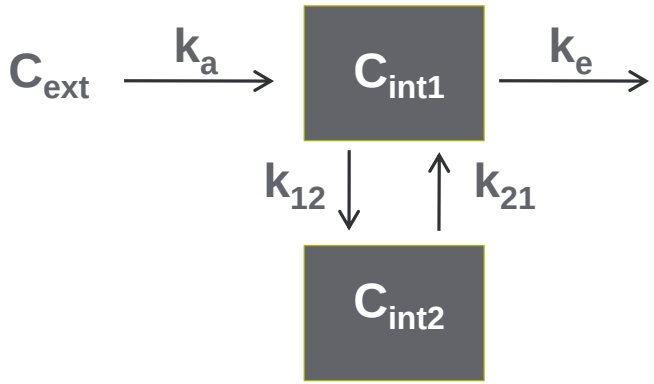
# A gallery of TK models: empirical

- One-compartment model
  - simple
  - organism treated as a ‘black box’


$$dC_{int}/dt = k_aC_{ext} - k_eC_{int}$$

- Multi-compartment model
  - central compartment (blood, highly perfused tissues including those responsible for biotransformation)
  - peripheral compartment (poorly perfused tissues, including fat)




$$dC_{int1}/dt = k_aC_{ext} - k_eC_{int} - k_{12}C_{int} + k_{21}C_{int2}$$

$$dC_{int2}/dt = k_{12}C_{int} - k_{21}C_{int2}$$



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# A gallery of TK models: mechanistic

- Physiologically Based Toxicokinetic (PBTK, PBPK) model

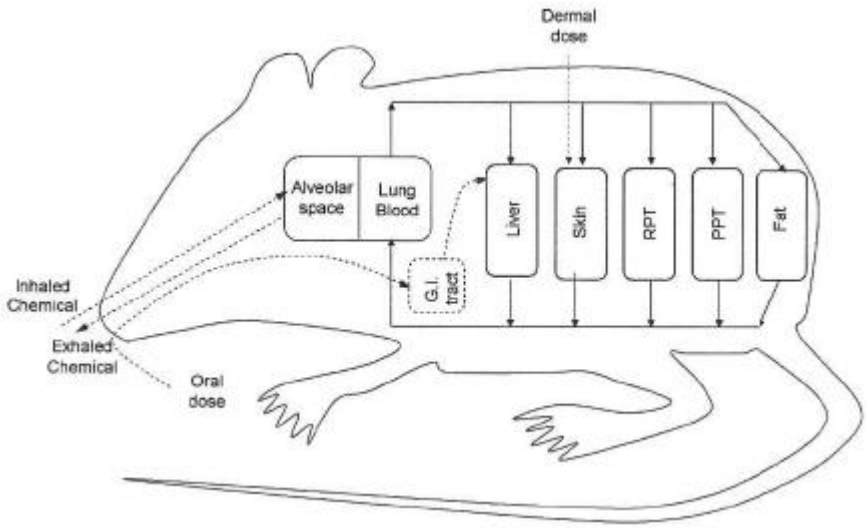



Fig. Schematic representation of a PBTK model for perchloroethylene in rat.

**PBTK parameters**: body weight, tissue volume, blood flows: cardiac output, alveolar ventilation, biochemical constants: Vmax, Km, tissue:blood partition coefficient, and many more ….

☹ Too many parameters with unknown values

☺ Species specific parameters known from literature

☹ New model needed for each compound and species

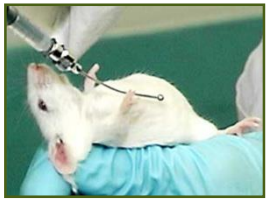
☺ Many compound specific parameters correlate with phys.-chem.; biochemical parameters from in-vitro tests

☹ Very resource demanding

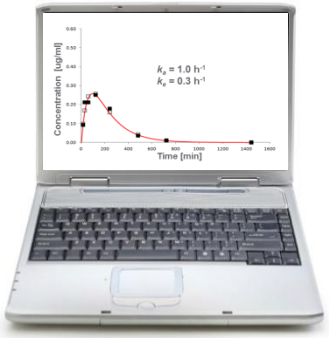
☺ Generic model structure possible

# Which approach to choose?

## Classical TK Modelling



Parameterisation



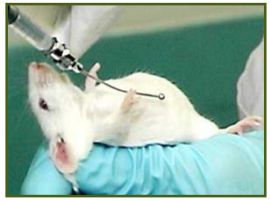

Application

## PBTK Modelling

Parameters

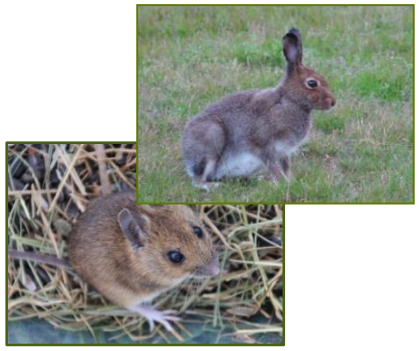
Validation

Calibration



Application

Prediction



# Aim of the project

Develop TK model to be used in bird and mammal risk assessment

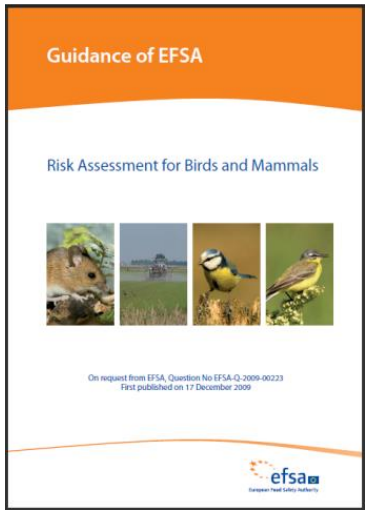
- Simple enough to be manageable and applicable across a range of exposure scenarios (and species)
- Sufficiently complex for representing all crucial processes
- **Parameterisation methods using standard regulatory data**

  (no additional tests required)

# TK models in EFSA Guidance

"*Within the registration process of PPP under Directive 91/414/ECC,* ***often data from metabolism studies (ADME) within rat, live-stock or hen are available****.*"

"*Where risk-refinement is necessary based on results from lower tier assessment,* ***'metabolism' data should be evaluated by the risk assessor for options to reduce the uncertainty associated with the risk assessment.***"

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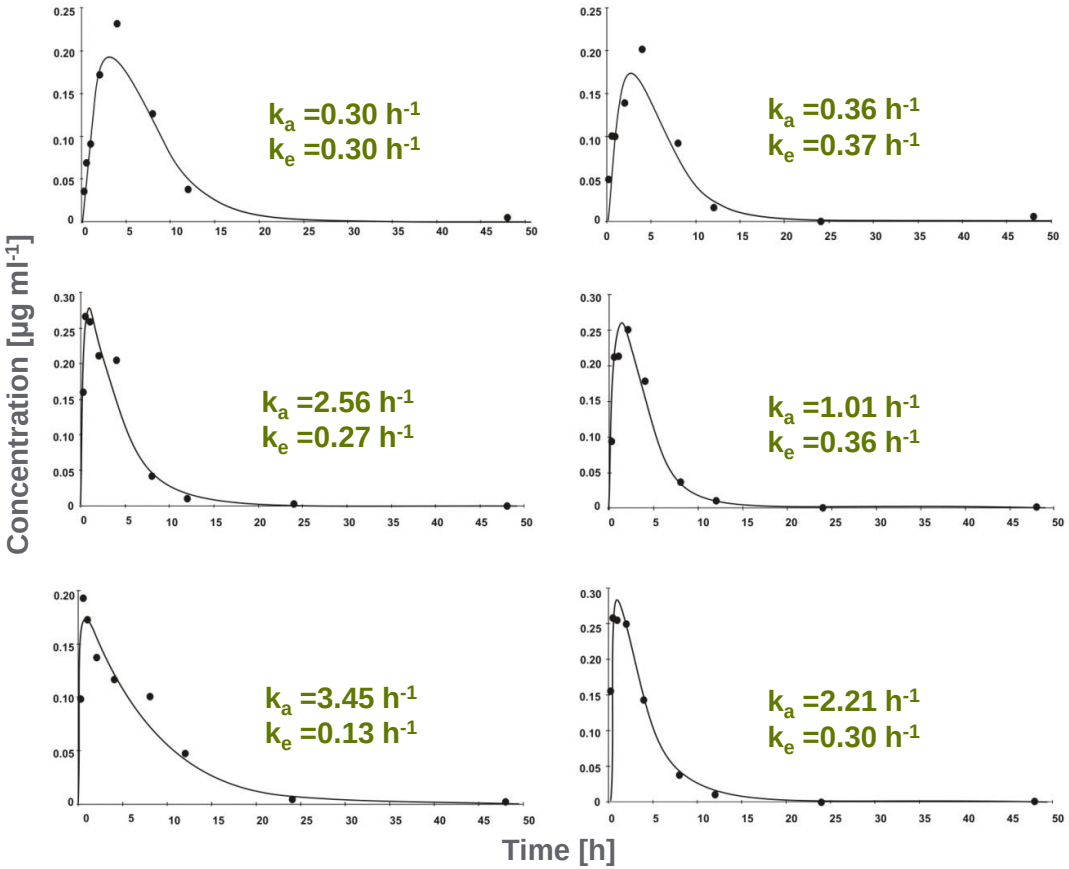
# Case study: metabolism data for an insecticide




**One-compartment model fits data best**

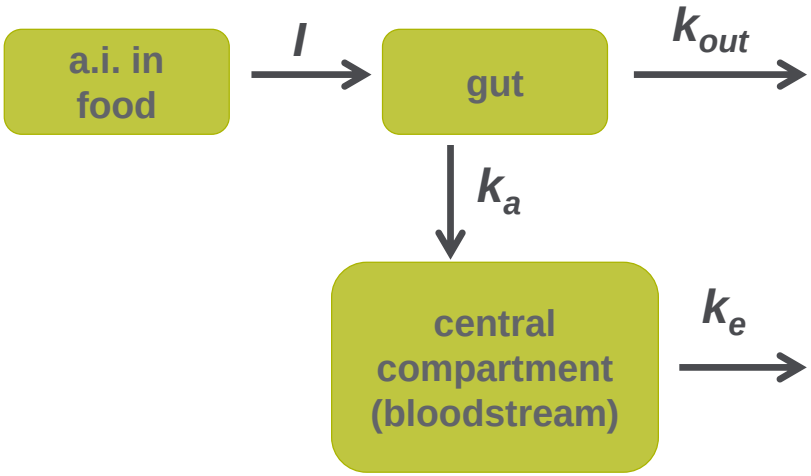
**Insecticide concentrations in blood highly correlated with concentrations in different tissues**

Up to 90% eliminated as parent compound through the urine

Fig.1. The concentration of an insecticide in blood of male rats administered 0.5 mg $kg^{-1}$ bw an insecticide. Lines are the one-compartment models fit to the experimental blood data. Note different scale on y axis.

WinNonlin software; comparison between different models based on residual plots and AIC. Model parameters estimated using Marquardt method.

# Case study: TK model (Body-burden model)




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

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

| | |
|---|---|
| $\Delta C$ | change in the gut $_{gut}$ or internal $_{int}$ concentration of pesticide in given time interval, [min$^{-1}$] |
| $I$ | intake rate [mg a.i. kg$^{-1}$ bw min$^{-1}$] |
| $k_{out}$ | 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$^{-1}$] |

# Case study: parameterization of TK model

## Kinetics parameters estimated from rat study based on radiolabeled test substance

| Parameters | intravenous exposure | | bolus gavage 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 | 2.20±0.93 | 3.2±0.29 | 0.78±0.32 | 1.6±0.71 | 0.71±0.73 | 2.00±1.37 |
| $k_e$ ($h^{-1}$) | 0.26±0.[illegible] | 0.50±0.11 | 0.23±0.09 | 0.23±0.13 | 0.34±0.034 | 0.25±0.0[illegible] | 0.28±0.12 | 0.18±0.06 | 0.25±0.11 | 0.19±0.06 |

# Case study: parameterization of TK model

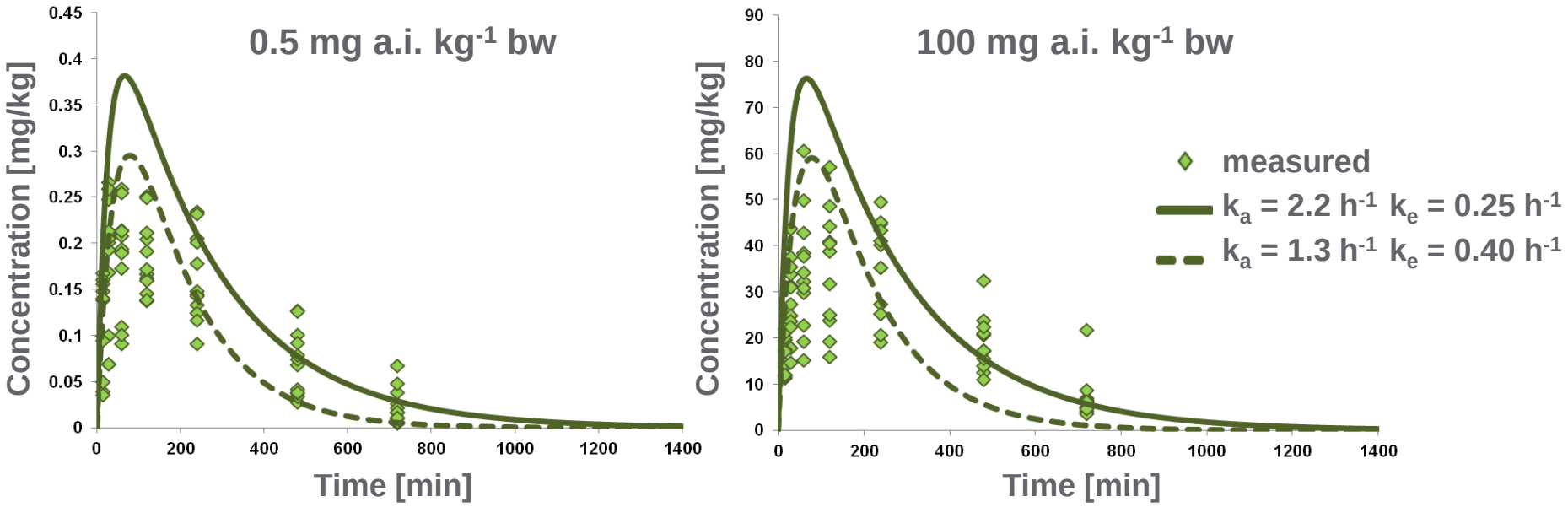
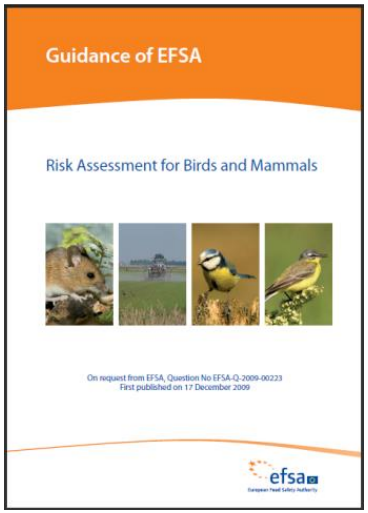



Figure 2. The concentration of an insecticide in blood of rats (points) after administration of 0.5 or 100 mg a.i. $kg^{-1}$ bw and model simulations (lines) for two extreme combinations of $k_a$ and $k_e$.

# Feeding pattern in EFSA Guidance

"*What rates of feeding occur in the field?*"

"***Do the feeding rates achieved in laboratory studies or assumed in model correspond to the maximum rates occurring in the field?*** "

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# Case study: different exposure simulations

**Intake rate of uncontaminated food [g diet $kg^{-1}$ bw $min^{-1}$] at 15-min time intervals over 2h**

| Time from start of feeding (min) | Control food [g diet $kg^{-1}$ bw] | | | | | Intake rate [g $kg^{-1}$ bw $min^{-1}$] |
|---|---|---|---|---|---|---|
| | C7 | C15 | C21 | C17 | ..... mean | mean |
| 0 | 0 | 0 | 0 | 0 | 0.0 | 0.00 |
| 15 | 10.9 | 7.8 | 6.3 | 5.6 | 9.2 | 0.61 |
| 30 | 14.1 | 11.3 | 6.3 | 9.4 | 14.2 | 0.33 |
| 45 | 20.3 | 16.9 | 6.8 | 13.8 | 17.5 | 0.22 |
| 60 | 23.5 | 24.5 | 10.3 | 16.4 | 20.5 | 0.20 |
| 75 | 26.7 | 28.1 | 15.5 | 18.9 | 23.6 | 0.21 |
| 90 | 28.8 | 28.1 | 19.8 | 19.7 | 25.1 | 0.10 |
| 105 | 28.8 | 31.9 | 20.7 | 19.7 | 26.8 | 0.11 |
| 120 | 28.8 | 31.9 | 20.7 | 20.6 | 27.1 | 0.02 |

| | |
|---|---|
| $LD_{50}$ eaten with constant intake rate over 120 min.: | 13.0 |

# Case study: different exposure simulations

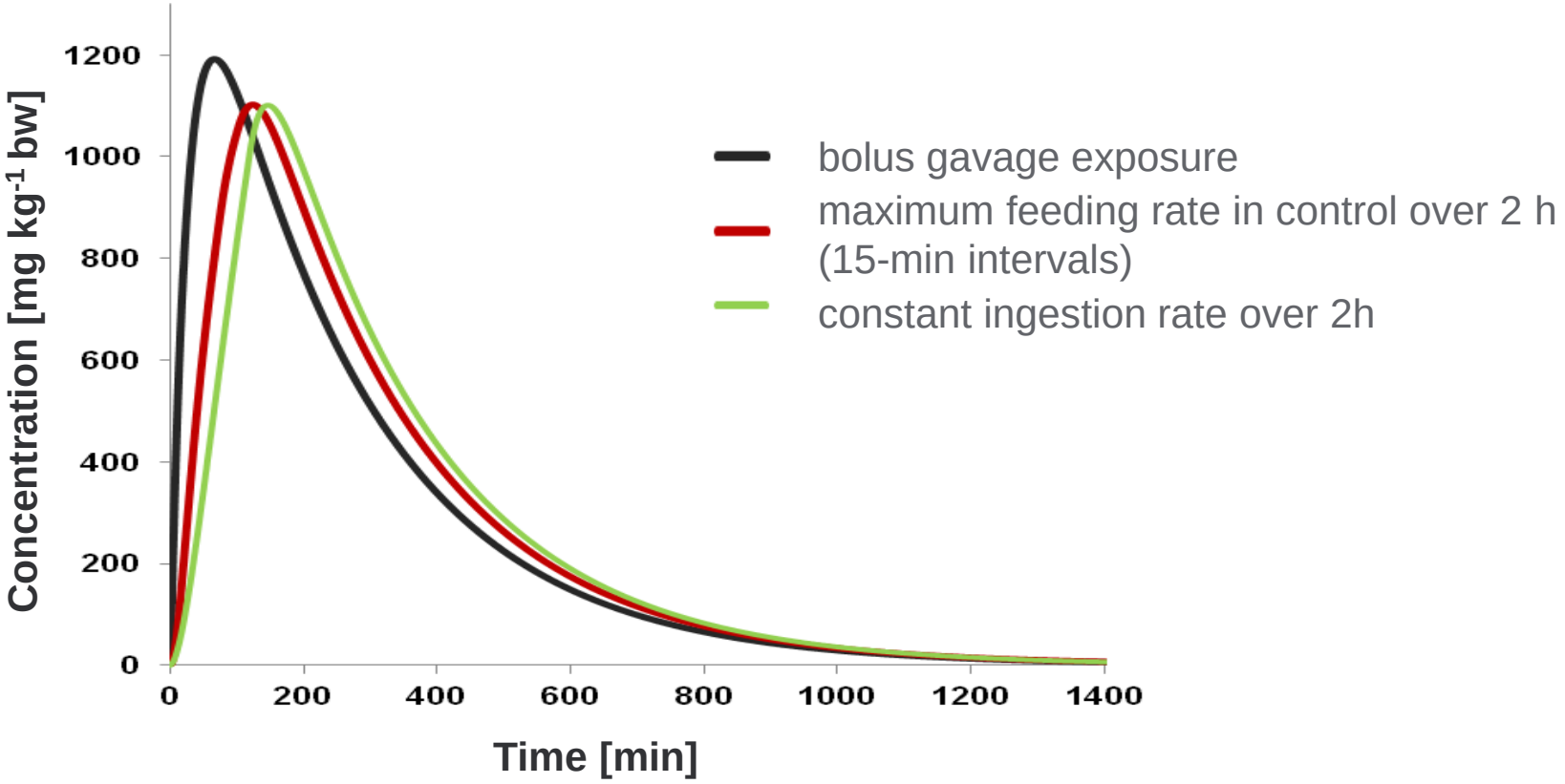
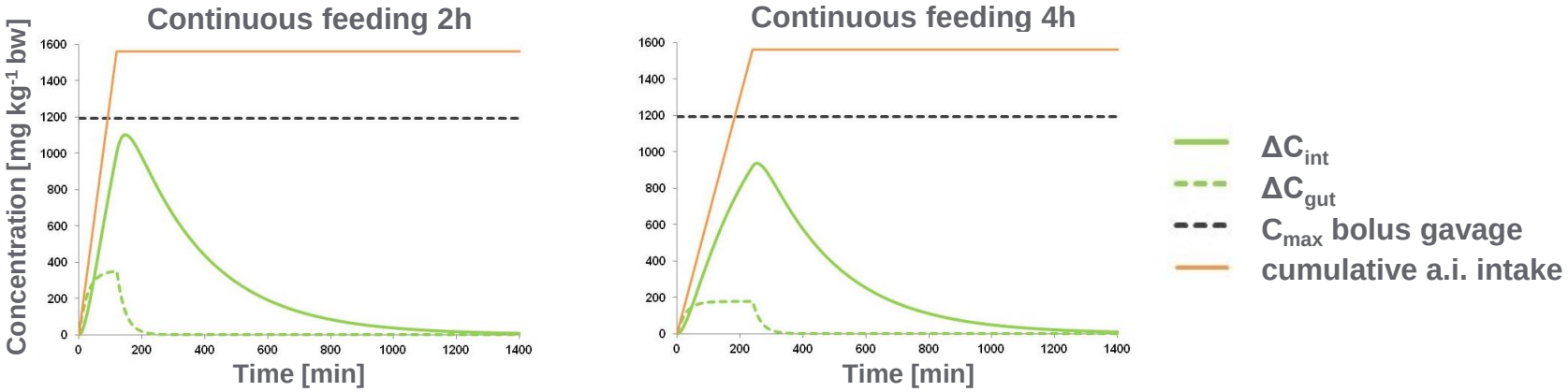
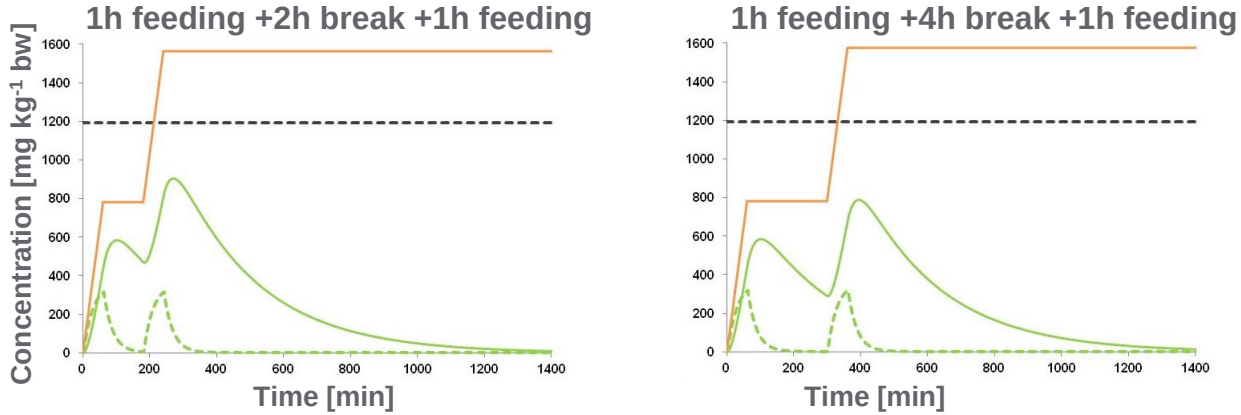



Fig. 3. The concentration of an insecticide in the body after eating $LD_{50}$ dose according to different intake rates; scenarios for $k_a$ = 2.2 and $k_e$ = 0.25

# Case study: $LD_{50}$ eaten with different feeding patterns




**The slower animals eat the lower internal maximum concentrations are reached**




**Breaks of low/no feeding activity after short feeding bouts affect internal concentration of pesticide**



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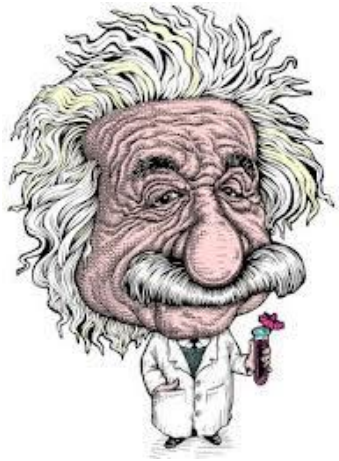
# Conclusions

- TK models are considered as a refinment tool for risk assessment in EU guidance for birds and mammals
- ADME data can be used to parameterize a body burden (or other TK) model
- Key assumptions which should be checked before using BB approaches:
  - Can kinetics be described as a first order process or is it more complex?
  - How many compartments should be included in the model?
  - Is it necessary to represent target organ(s) as separate compartment(s) or is the toxicant concentration in systemic circulation (blood) sufficient?
- BB model based on total radioactivity, so metabolites are not characterized separately - PBTK models may be sometimes preferred
- Behavioural responses may moderate exposure - taking into account behavioural responses, timescales of exposure and kinetics improve risk assessment

# Conclusions

- Choice between approaches (model structure and type) depends on intended use – make model only as complex as needed



Everything should be made as
simple as possible, but not simpler.

– Albert Einstein

*Thank you for your attention*

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