Modelling transfer of dioxins from feed to eggs

experimental data model building identification analysis

Kees Kan; ASG, Lelystad: laying hen experimentation, sampling
Wim Traag, Ron Hoogenboom; RIKILT, Wageningen: dioxins analysis
Marco Zeilmaker, Jan van Eijkeren; RIVM, Bilthoven: transfer modelling

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Modelling in three stages:

- **Experimental data:**

  no data obtained, no knowledge gained

  ~~**data obtained, knowledge gained**~~

- **Model building:**

  PBPK, classical compartment, classical kinetic

  do not stick to paradigms

- **Identification analysis**

  which parameters can be quantified, which not

  where to trigger, what to sample

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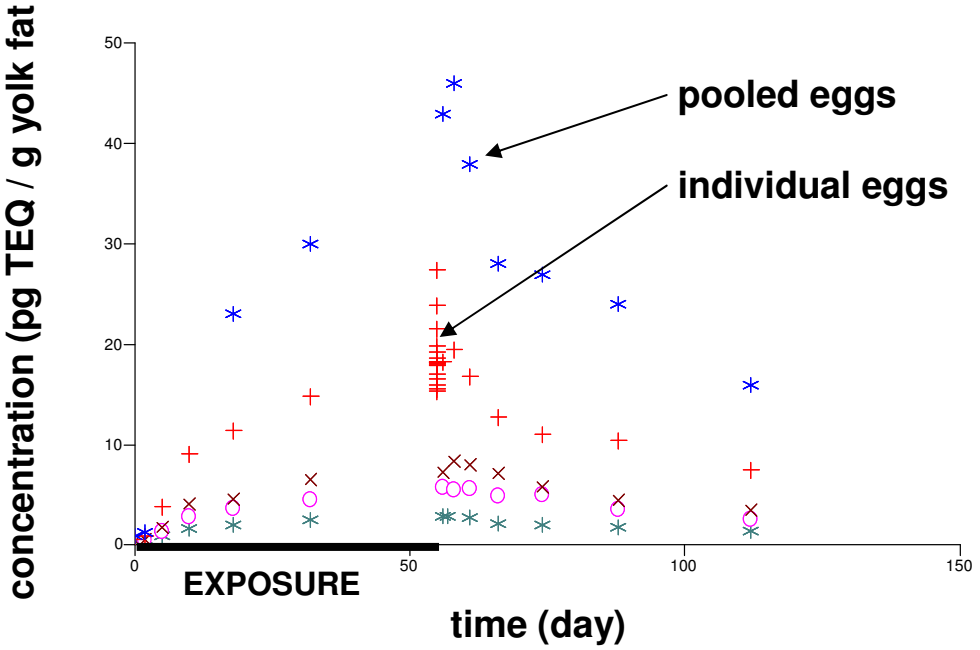
Experimental data

KINETICS OF SUSTAINED ORAL ADMINISTRATION

- **fast rate initial phase**
- **slow rate terminal phase**
- **interindividual variability**

NOTE:

- **sampling scheme**
- **experimental duration**
- **pooled eggs**



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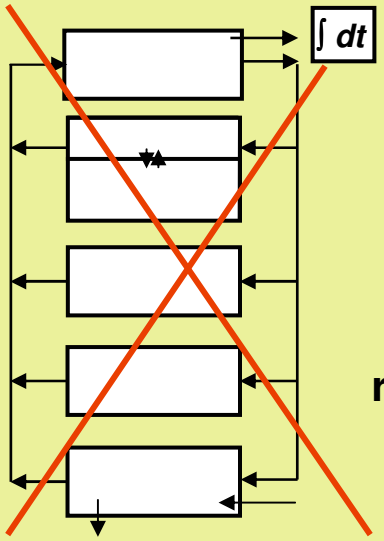
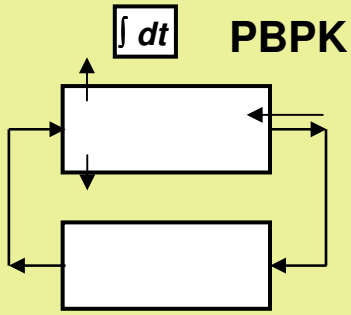
Model building history

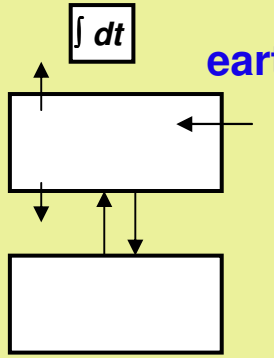


model reduction



PBPK heaven

parameter reduction

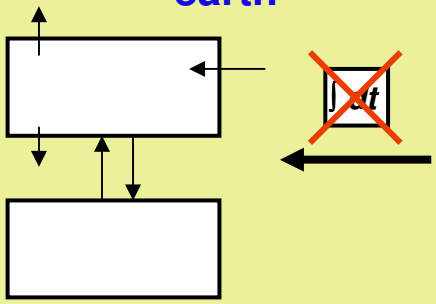


earth

data fitting

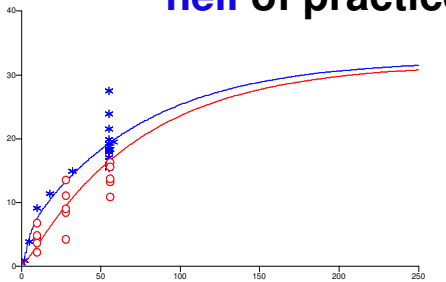
?

earth



parameter identification problem

hell of practice



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Model reduction

PBPK modelling approach: from 5 to 2 compartments

- only sparse and outdated data on body composition
- no data on cardiac output and regional blood flow
- no data on lipid content and lipid composition of tissues (tissue:blood partition coefficients)
- compound property directed reduction: fat compartment for lipophilic compounds

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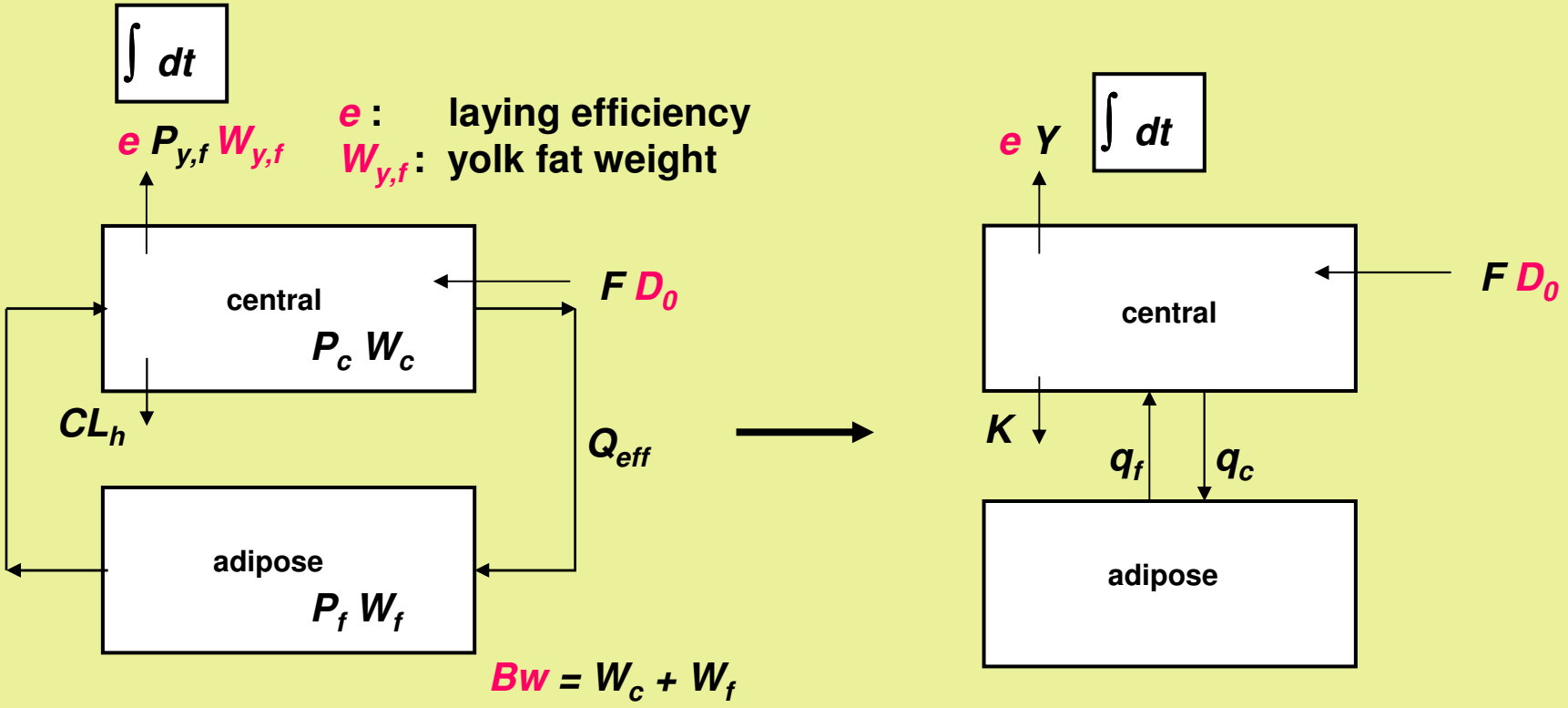
Parameter reduction



$$q_c = \frac{Q_{eff}}{P_c W_c} \qquad q_f = \frac{Q_{eff}}{P_f W_f} \qquad Y = \frac{P_{y,f} W_{y,f}}{P_c W_c} \qquad K = \frac{CL_h}{P_c W_c}$$

total elimination $R = eY + K$

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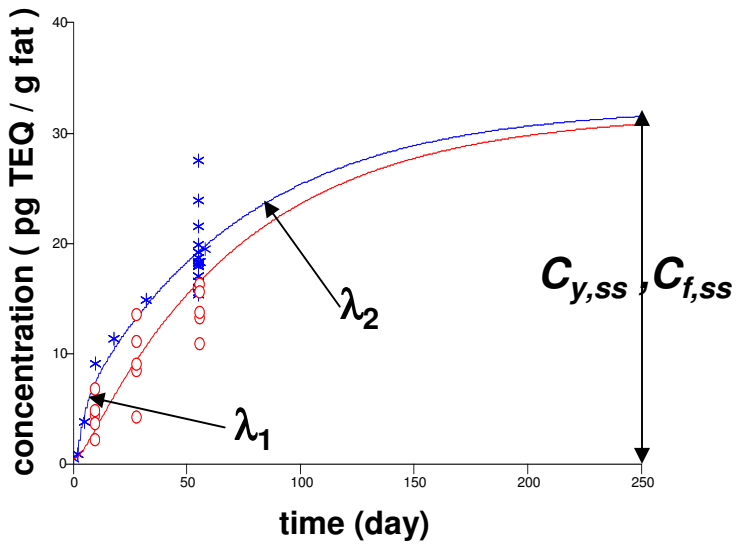
Data fitting

Eggs: $C_{y,f} = C_{y,ss} \left(1 - \left(a \times e^{\lambda_1 t} + \left(1 - a \right) \times e^{\lambda_2 t} \right) \right)$ ⟶ $\int dt$

Fat: $C_f = C_{f,ss} \left(1 - \left(b \times e^{\lambda_1 t} + \left(1 - b \right) \times e^{\lambda_2 t} \right) \right)$



$$\lambda_1 = -\left(q_c + q_f + R + \sqrt{\left((q_c + q_f + R)^2 - 4\, q_f\, R \right)} \right) / 2$$

$$\lambda_2 = -\left(q_c + q_f + R - \sqrt{\left((q_c + q_f + R)^2 - 4\, q_f\, R \right)} \right) / 2$$

$$a = \frac{\lambda_2 + R}{\lambda_1 - \lambda_2} \qquad b = \frac{\lambda_2}{\lambda_1 - \lambda_2}$$

$$C_{y,ss} = \frac{Y}{W_{y,f}} \frac{F\, D_0}{R} \qquad C_{f,ss} = \frac{q_c}{q_f} \frac{1}{W_f} \frac{F\, D_0}{R}$$

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Parameter identification

$\lambda_1 + \lambda_2 = -(q_c + q_f + R)$

$\lambda_1 \times \lambda_2 = q_f \times R$

$$a = \frac{\lambda_1 + R}{\lambda_1 - \lambda_2}$$

UNCONDITIONAL

λ_1	q_c
λ_2	q_f
a	R

CONDITIONAL

R

$C_{y,ss}$

$C_{f,ss}$

constant	$c_1 = R = eY + K$
constant	$c_2 = Y \times F$
constant	$c_3 = F / W_f$

3 ↔ 4

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Parameter fitting

TRICK:

set $K = 0$, fit parameters: Y_{max} , F_{min} , $W_{f,min}$

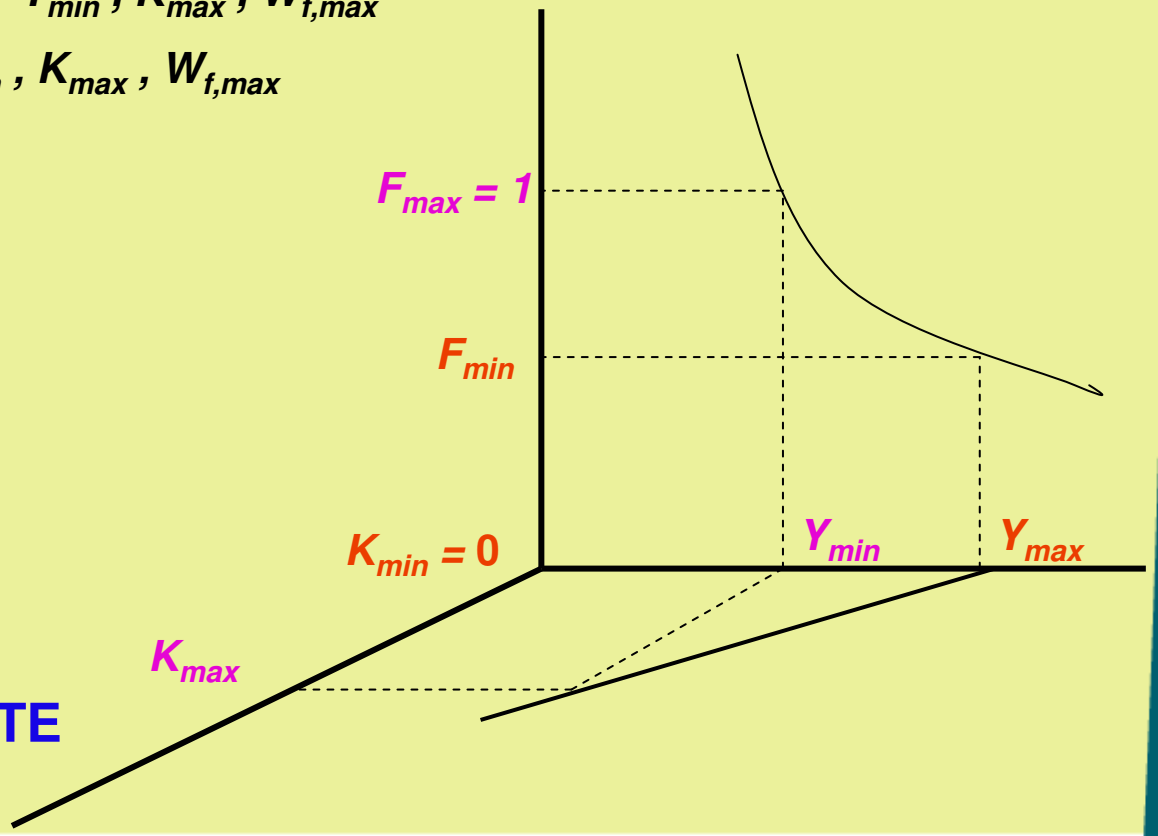
calculate, assuming $F_{max} = 1$, Y_{min} , K_{max} , $W_{f,max}$

validate: setting $F = 1$, fit Y_{min} , K_{max} , $W_{f,max}$

RESULT:

Y: [0.043, 0.055] day^{-1}
K: [0, 0.011] day^{-1}
F: [0.78, 1]
W_f : [0.23, 0.29] kg

CALCULATE = VALIDATE



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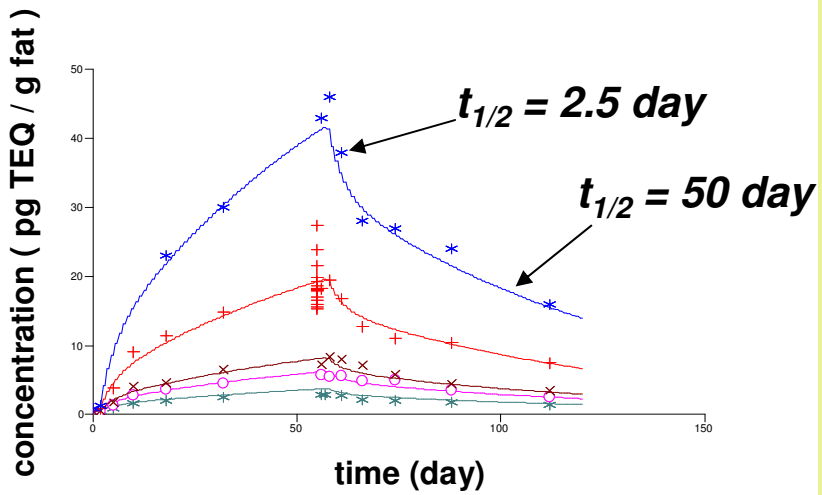
Modelling result

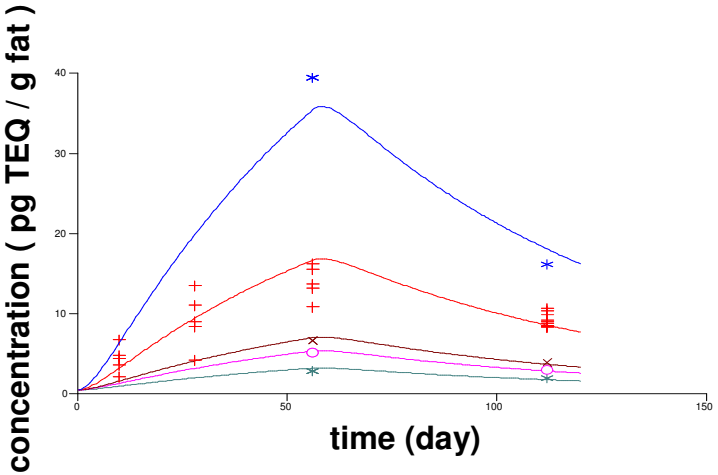


Validation:

- different subgroups : dioxins, furans, mono-ortho PCBs, non-ortho PCBs
- 10 fold higher exposure & different dioxins composition
- non-dioxin like PCBs

Application:

EU-limits in eggs (3 pg TEQ / g yolk fat) and in feed (0.75 ng TEQ / kg feed) do not comply:
should be 0.2 ng TEQ / kg feed



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Conclusions

- Modelling transfer of dioxins from feed to eggs succeeded thanks to:
  - careful experimental set-up
  - justified choice of kind of model
  - parameter identification analysis

- The model was successfully
  - verified on other data
  - applied to dioxin limits comparison in eggs and feed

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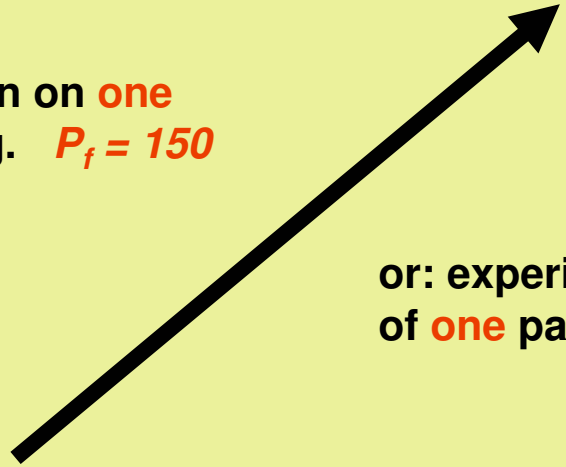
REDEMPTION

PBPK heaven: Q_{eff} CL_h P_c $P_{y,f} = P_f$

powerful assumption on one parameter value, e.g. $P_f = 150$



or: experimentally determination of one parameter value, e.g. P_f

earth: q_c q_f Y K

REDEMPTION

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J.C.H. van Eijkeren, M.J. Zeilmaker, C.A. Kan, W.A. Traag & L.A.P. Hoogenboom;
A toxicokinetic model for the carry-over of dioxins and PCBs from feed and soil to eggs;
Food Additives and Contaminants; **23** (2006) 509-517

L.A.P. Hoogenboom, C.A. Kan, M.J. Zeilmaker, J.C.H. van Eijkeren, & W.A. Traag;
Carry-over of dioxins and PCBs from feed and soil to eggs at low contamination levels –
Influence of mycotoxin binders on the carry over from feed to eggs;
Food Additives and Contaminants; **23** (2006) 518-527

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