Livestock: which transfer models to use

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Workshop Feed Risk Assessment-Chemical Safety

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Transfer modeling: Why?

- Feed crisis: feed contamination(concentrate, grass, soil)
- Structural: environmental pollution
- Incidental : fires (monitoring results)

- predicted concentration in edible products of animal origin (milk, eggs, meat)
- risk assessment
- duration of increase above legal food standards
- effect on human dietary exposure
- evaluation of health risk for consumers

Transfer modeling: How?

- Computer model for parent compound/metabolites
- Core of model:
  - Absorption
  - Distribution
  - Metabolism/Excretion
- Comparison with experimental data (calibration/verification)
- Data sources:
  - Literature (models and data)
  - Animal studies (RIKILT/NIFES/BfR)
- In house model development

Transfer modeling: How?

Generic concept: Physiologically Based Kinetic modeling

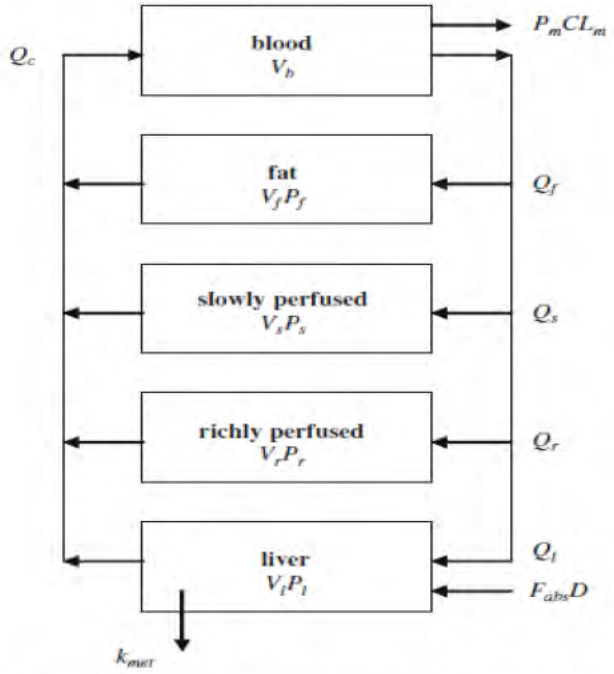
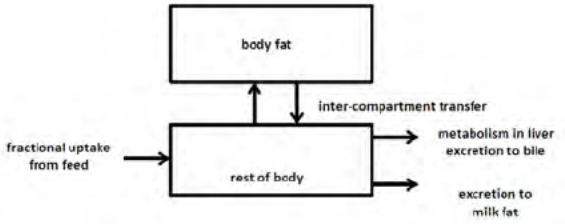


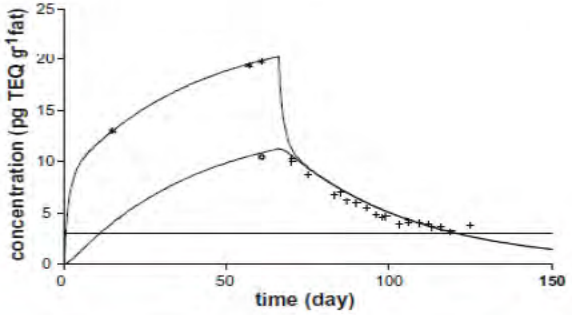
Fig. 2. Scheme of the applied PB-PK model. V is for compartment volume, Q for regional blood flow and P for compartment:blood partition coefficient. Dioxins are cleared from blood to milk proportional to milk fat production CL_m and milk fat:blood partition P_m. Furthermore, dioxins are cleared by metabolic clearance k_{met}. A fraction F_{abs} of the dose of dioxins enters the liver via the portal vein.

Transfer modeling: How?

- Always look at your data!
- Narrow down when possible!
- When necessary incorporate biological mechanisms
  - inducible binding proteins (Cd)
  - toxic metabolites (Aflatoxin B1/Toxaphene)

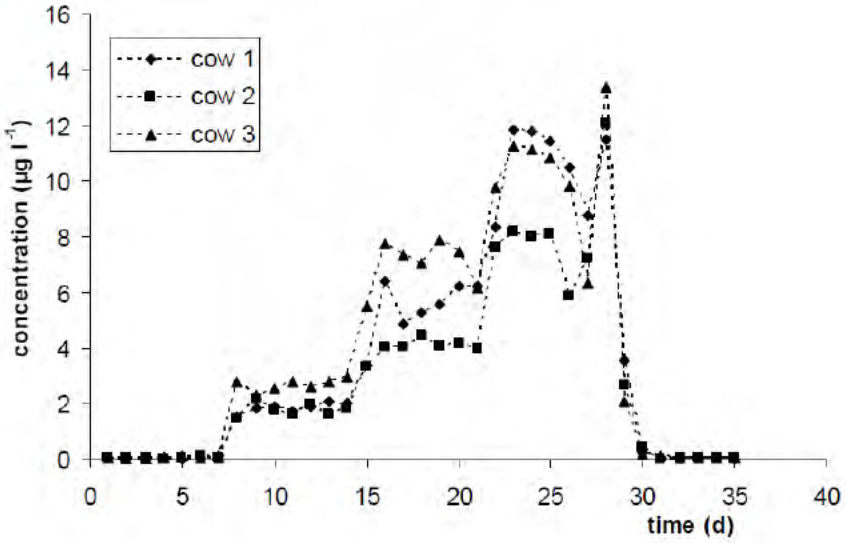
- Quick stable level in food: "steady state kinetics"
- Distribution via the blood is relative fast and body can be divided into two "lumped" organ compartments:





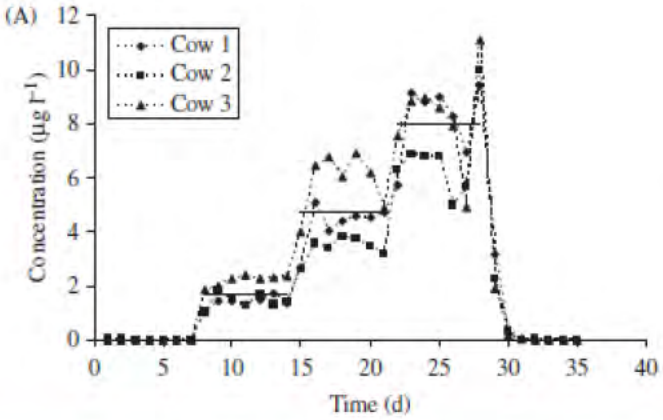
Pyrrolizidine alkaloids: Jacoline (cattle)

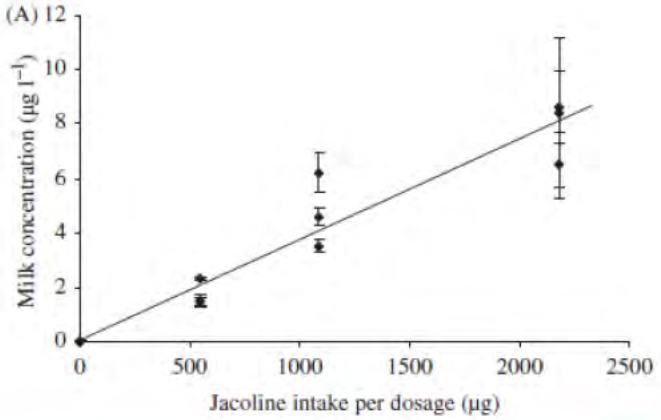
- Rapid "steady state" excretion to milk



Pyrrolizidine alkaloids: Jacoline (cattle)

- Data: Jacoline in milk (RIKILT)
- Exposure duration:
  - week 1: control feed
  - weeks 2-4: 2 x 25, 50 or 100 g
  - week 5: control feed
- Model: Feed ⟶ Milk regression equation





Cadmium (growing pig)

- Very low absorption from feed
- Accumulation in liver and kidney
- Mechanism: binding to inducible proteins (metallothioneins, MT)

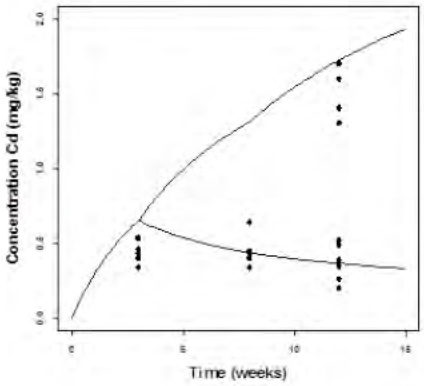
- Literature: 13 compartment model for Cd in livestock
- Analysis: Cd transfer to kidney and liver is an irreversible process
- Analysis: transfer reduced to one single transfer equation!

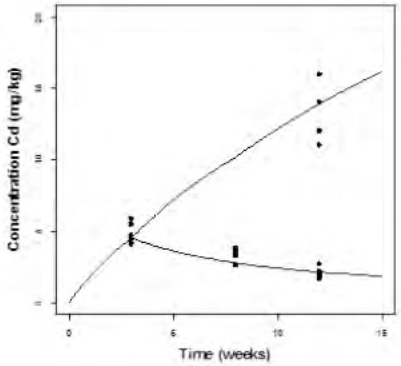
- Transfer equation incorporates Cd induced MT

Cadmium (growing pig)

- Data: Cd and MT in kidney (RIKILT)
- Exposure duration: 3 or 12 weeks
- Exposure: 1 or 10 mg/kg feed

- Model: Feed ⟶ Kidney mechanistic transfer equation

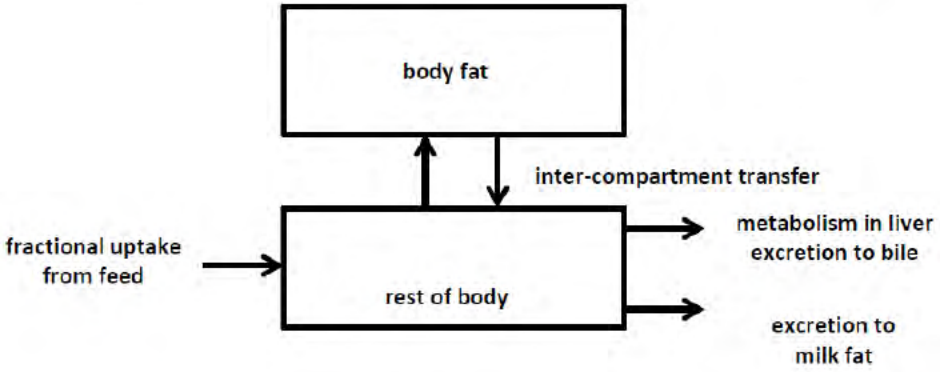




Dioxins (laying hen)

- High absorption from feed
- High affinity for body fat (adipose tissue, organ fat, milk fat, egg yolk fat)
- Distribution mechanism: lipid partitioning

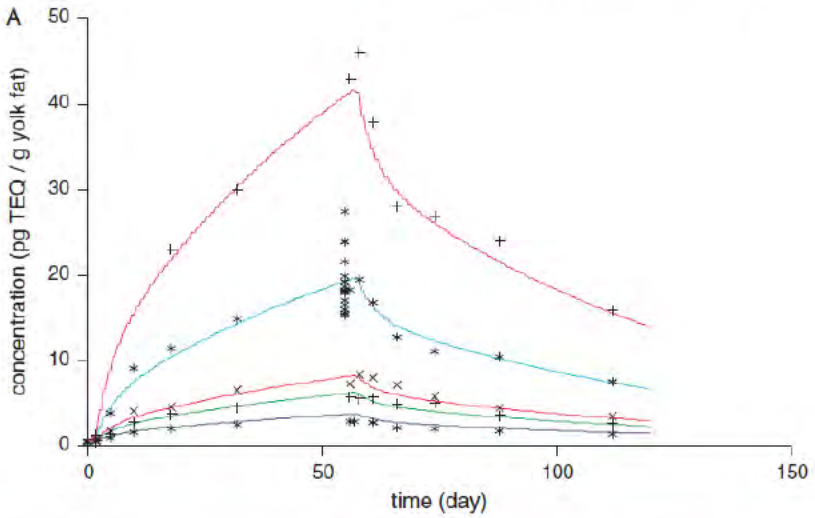
Feed → Animal → Milk/Egg



Dioxins (laying hen)

- Data: TEQ in egg yolk fat (RIKILT)
- Exposure duration: 56 days (+), 56 days (-)
- Exposure: 0.34 – 3.95 ng TEQ/kg feed

- Model: 2-compartment PBPK



RIVM transfer modeling: Current status

• Dioxins	dairy cattle	milk; body fat
	pig	body fat
	laying hen	egg, body fat
• Metals (Cd, As, Hg)	dairy cattle	kidney, liver
	growing pig	kidney liver
• PFOS/PFOA	fish (trout)	meat
	dairy cattle	milk, meat
• PAs	dairy cattle	milk
• Melamine	laying hen	egg
	pig	meat
• Pesticides	laying hen	egg, body fat
• HBCDD	Atlantic salmon	meat
• Toxaphene + metab.	Atlantic salmon	meat

RIVM transfer modeling: Future plans

- Make RIVM models accessible and usable for the rest of the world
- Sharing of RIVM models via web-based platform (demo)
- https://demo.carry-over.rivm.nl/

- Invitation to share transfer models/collaborate in designing transfer experiments
- Web-based discussion platform for transfer modeling

- Questions:
  - feasible idea?
  - conditions/criteria?
  - needs?
  - others?

Thank you for your attention

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