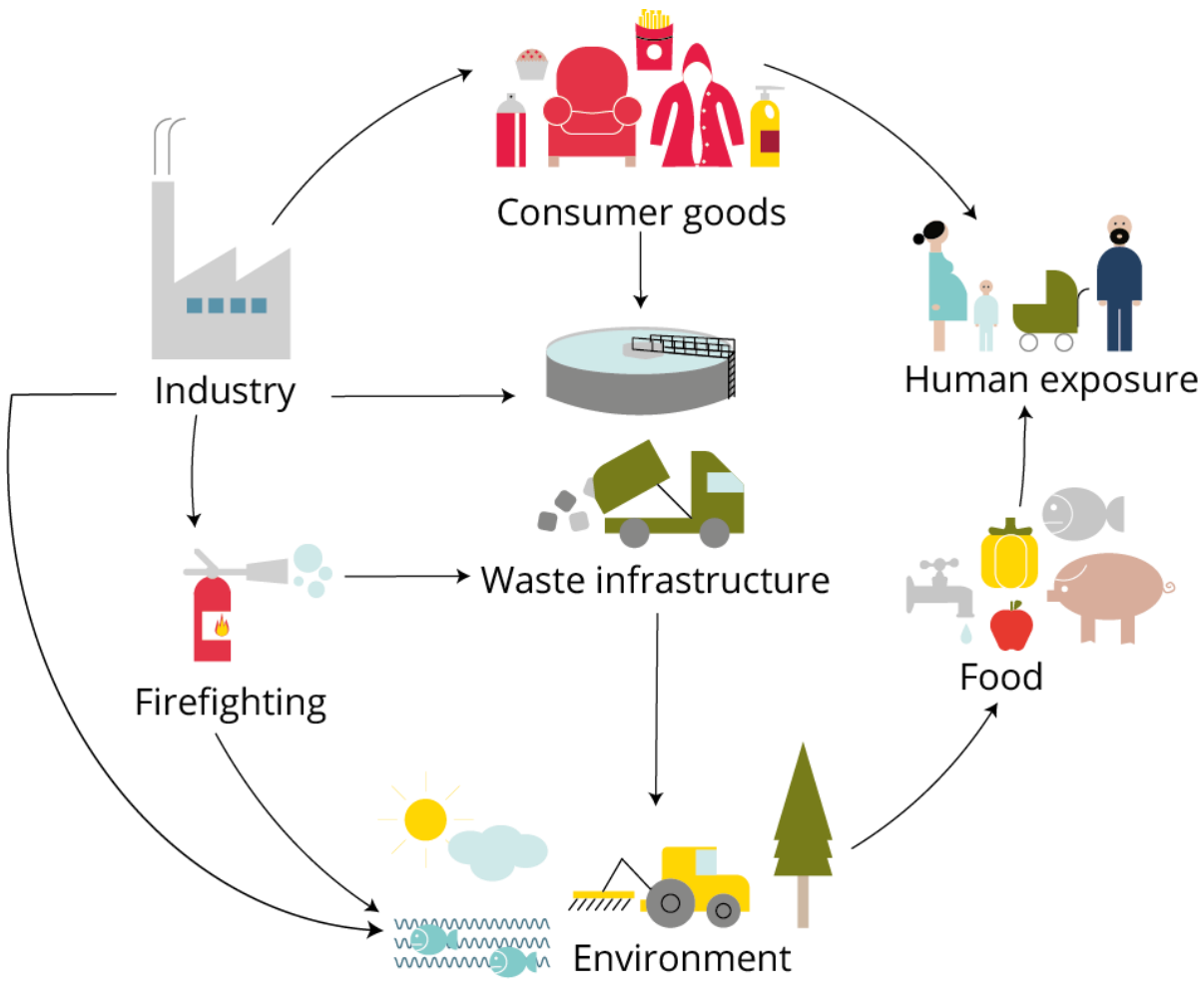
Generic physiologically based kinetic models in livestock

A case study for PFOS

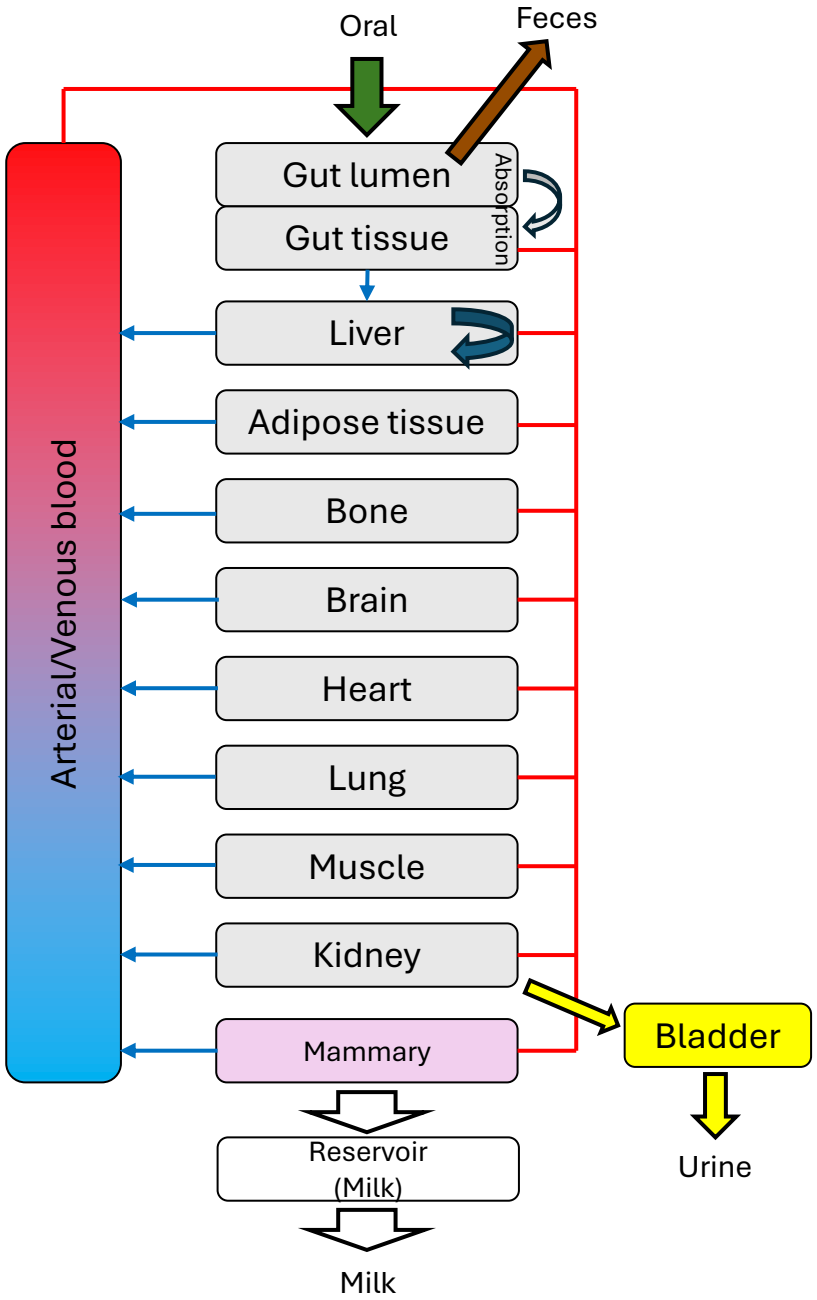
David Inauen
Utrecht Universiteit

PFAS



https://www.eea.europa.eu/publications/emerging-chemical-risks-in-europe/emerging-chemical-risks-in-europe

Physiologically based kinetic (PBK) model



Uptake, distribution, metabolism and excretion of a chemical over time

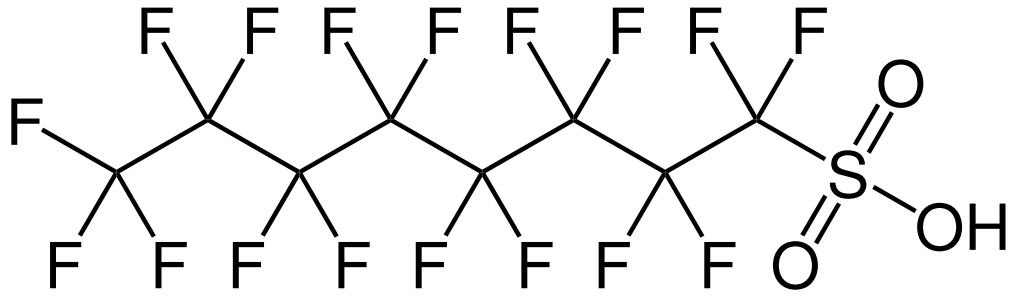
$$C_{tissue} = A_{tissue}/V_{tissue}$$

$$\frac{dA_{tissue}}{dt} = Q_{tissue} * (C_{art} - CV_{tissue})$$

$$CV_{tissue} = C_{tissue}/PC_{tissue} * BP$$

Generic model:
Not animal species or chemical specific

Perfluorooctanesulfonic acid (PFOS)



Rosato et al, 2024

Long environmental half-life
Mean half-life in human: 4.8 years

Kinetics of PFOS

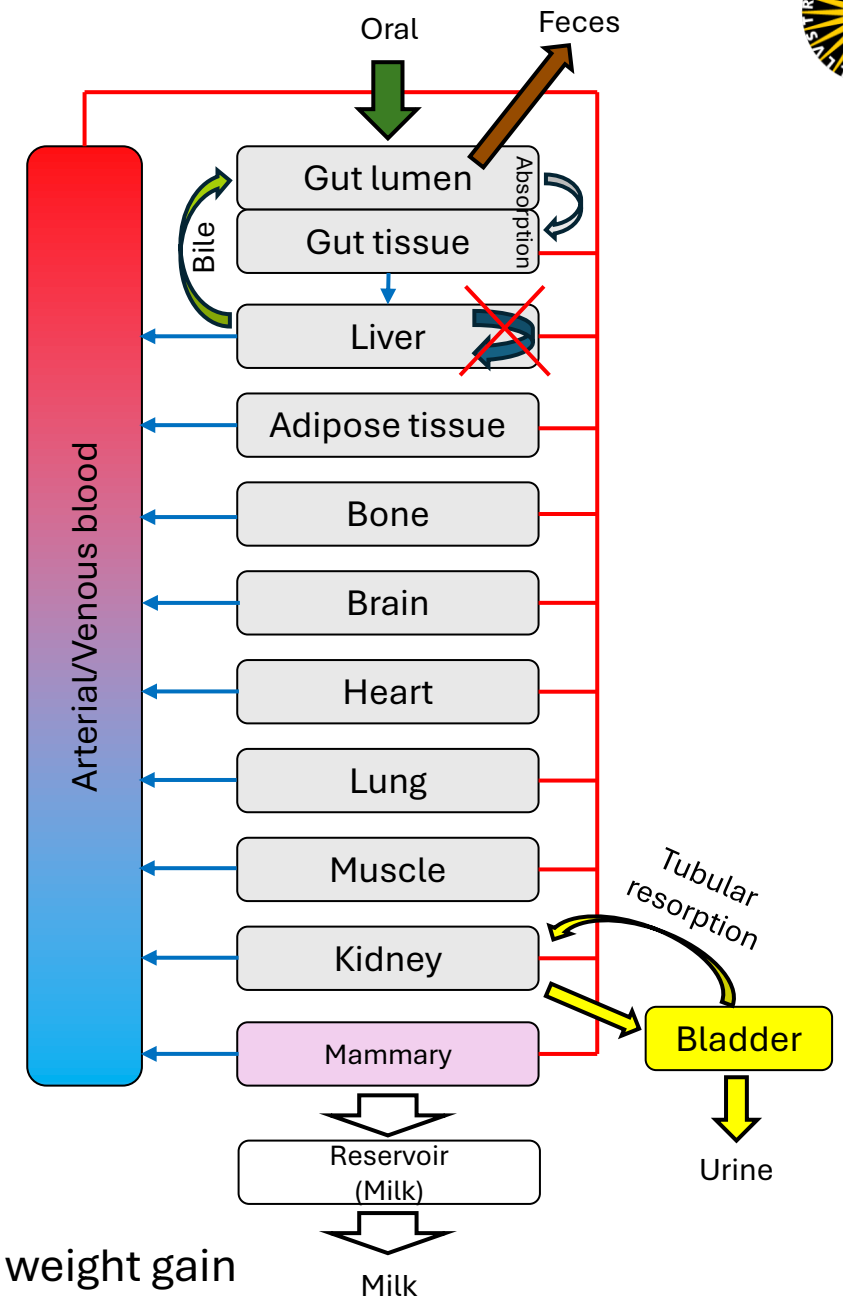
Highly plasma protein bound
→ Barely any liver metabolism

Enterohepatic recycling
→ Bile flow back to intestines
- Reabsorption through intestines
- Fecal excretion

Tubular urinary resorption
→ Limited urinary excretion

Long half-life in the body
Half-life in livestock up to years

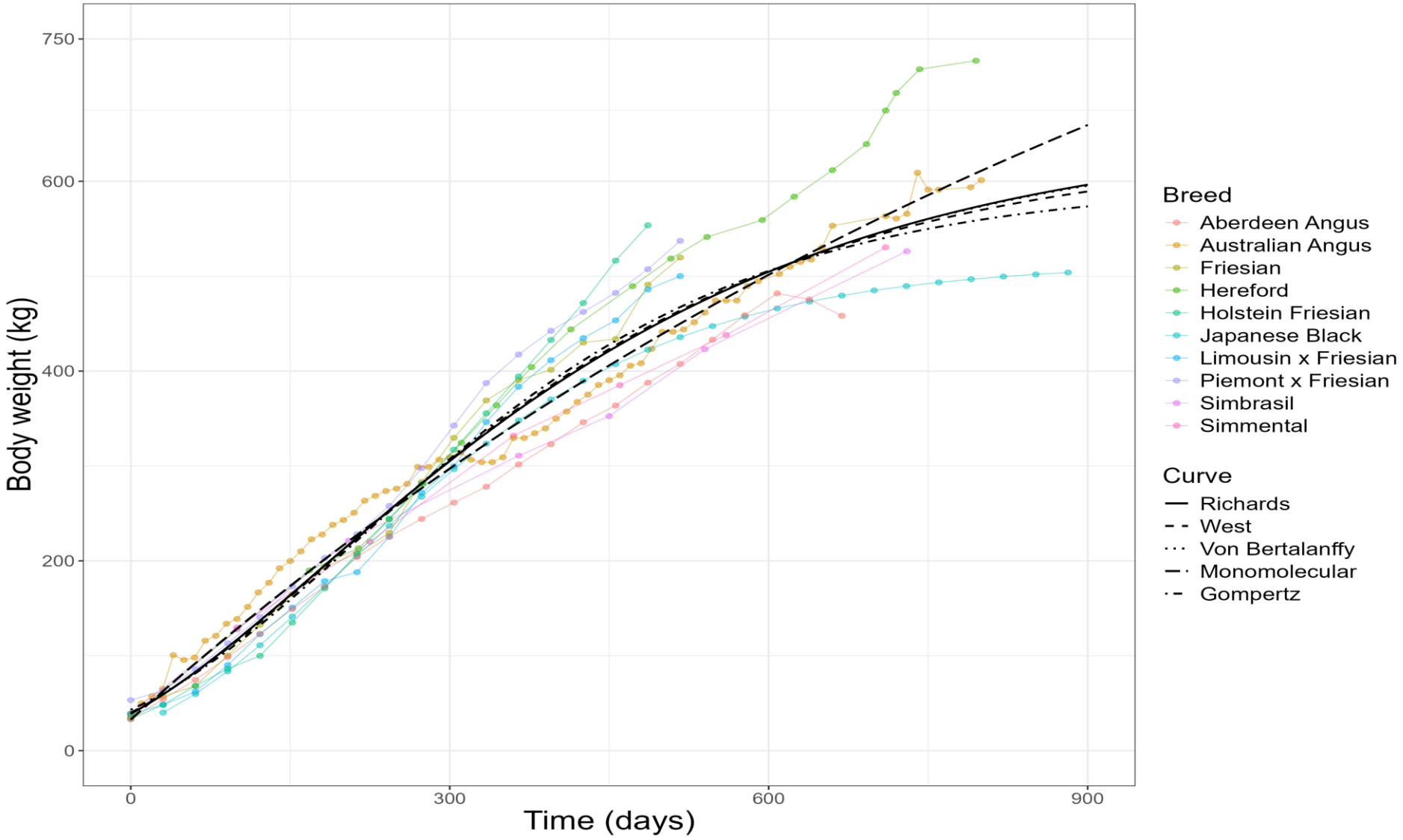
Transfer into milk and eggs
- Low transfer into milk
- High transfer into eggs



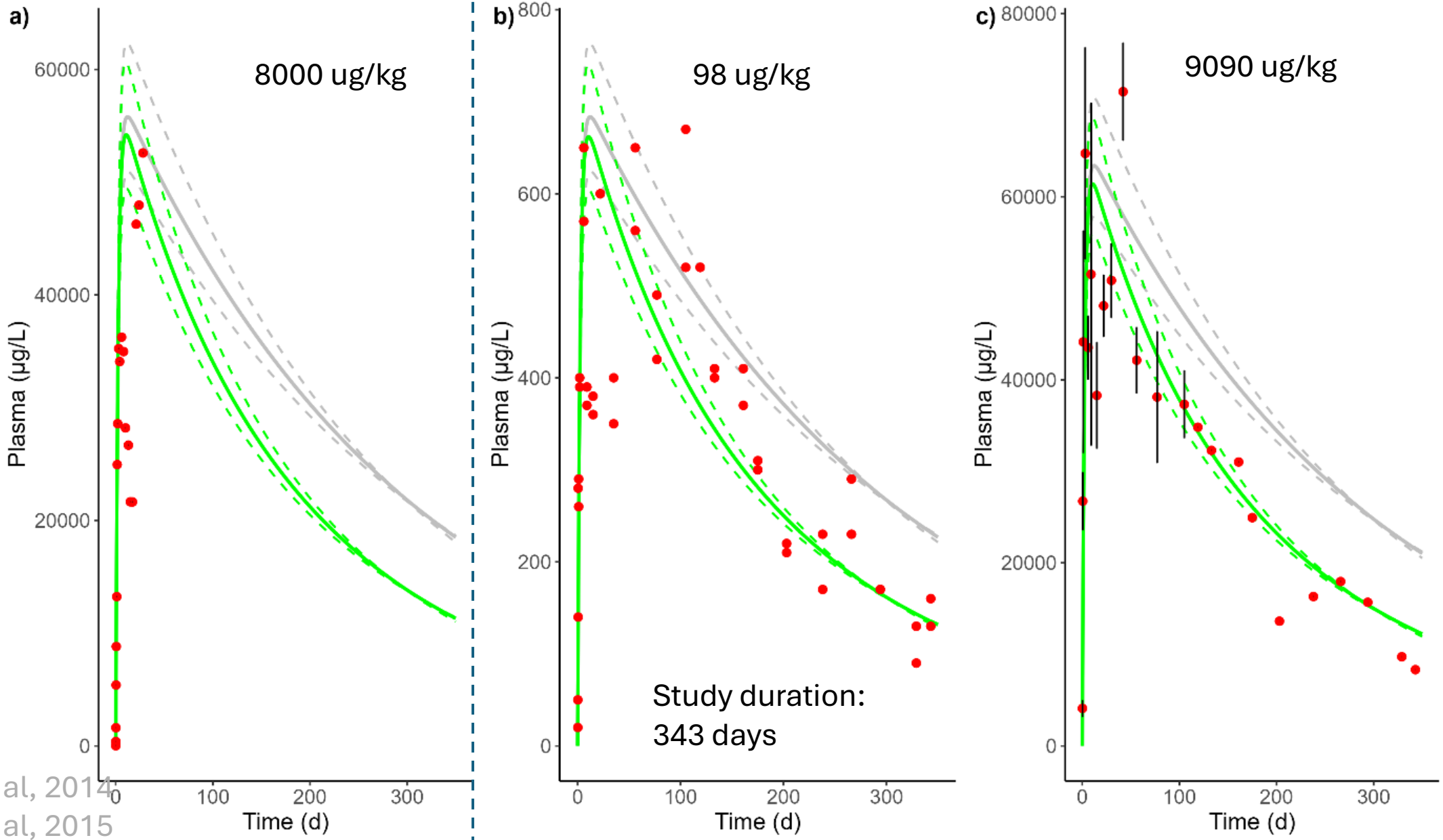
Jones et al, 2003
Death et al, 2021
EPA 2014

→ Concentrations affected by body weight gain

Growth curves (Cattle)



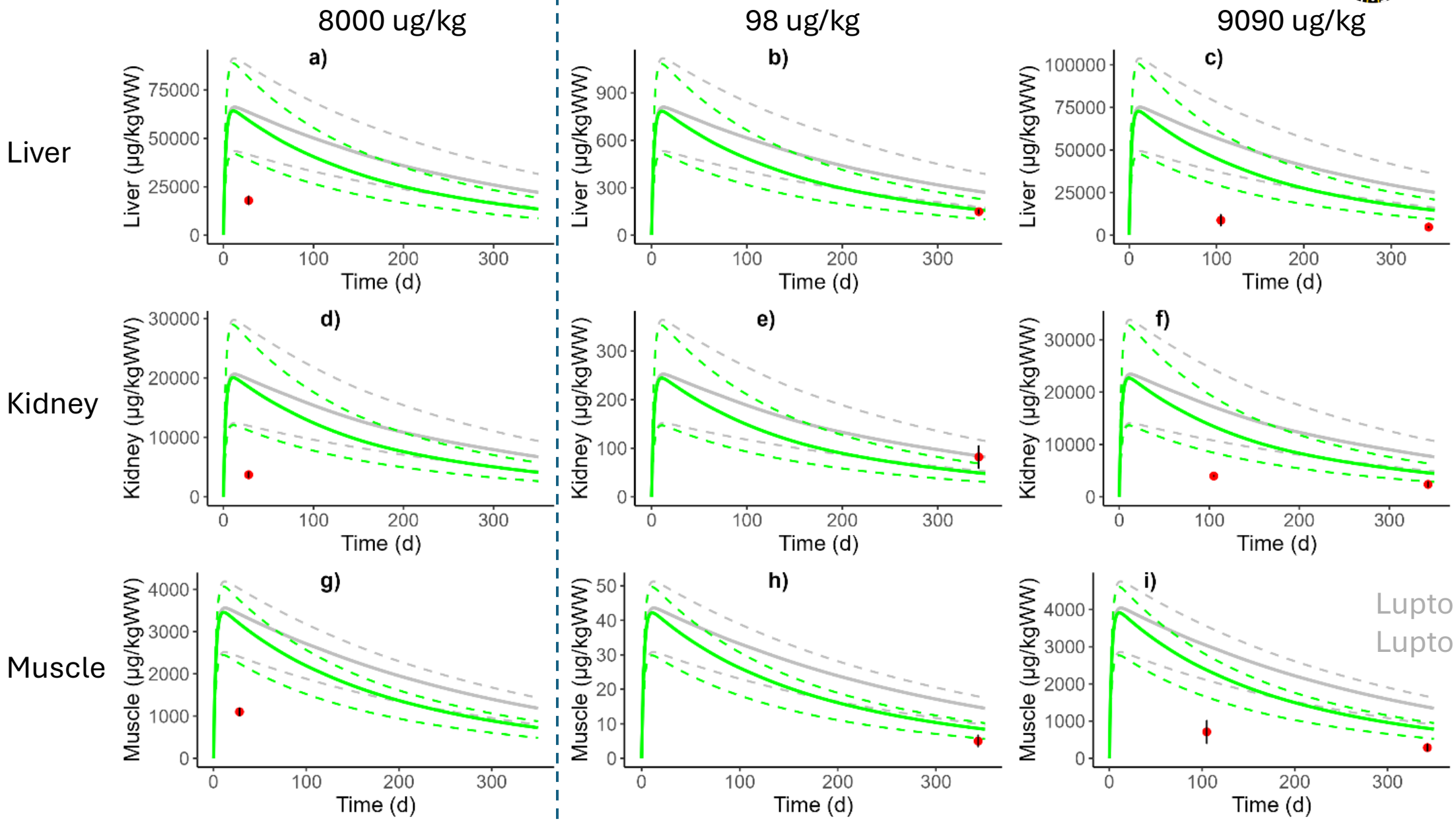
Results cattle plasma



Lupton et al, 2014
Lupton et al, 2015

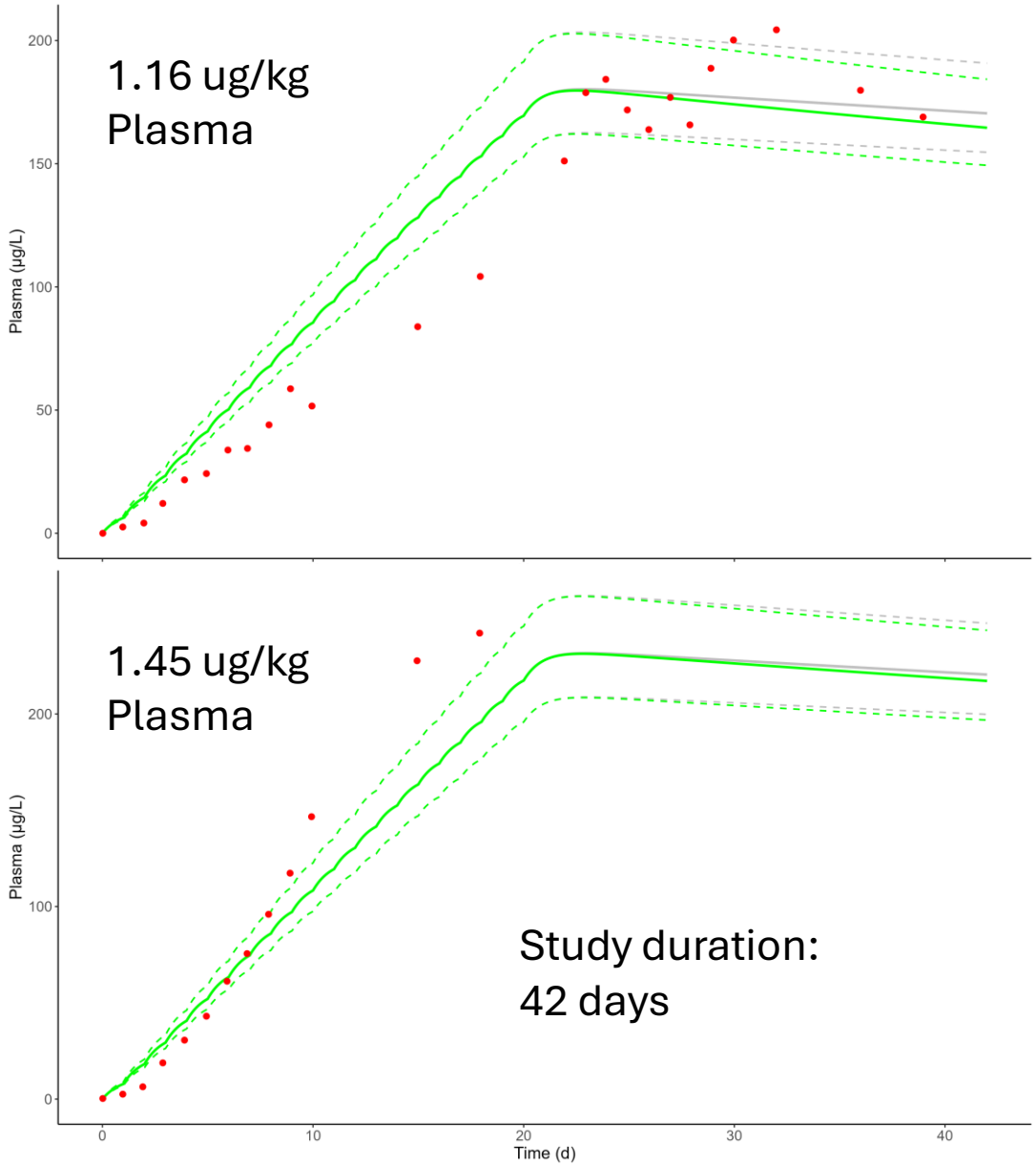
Results cattle tissue

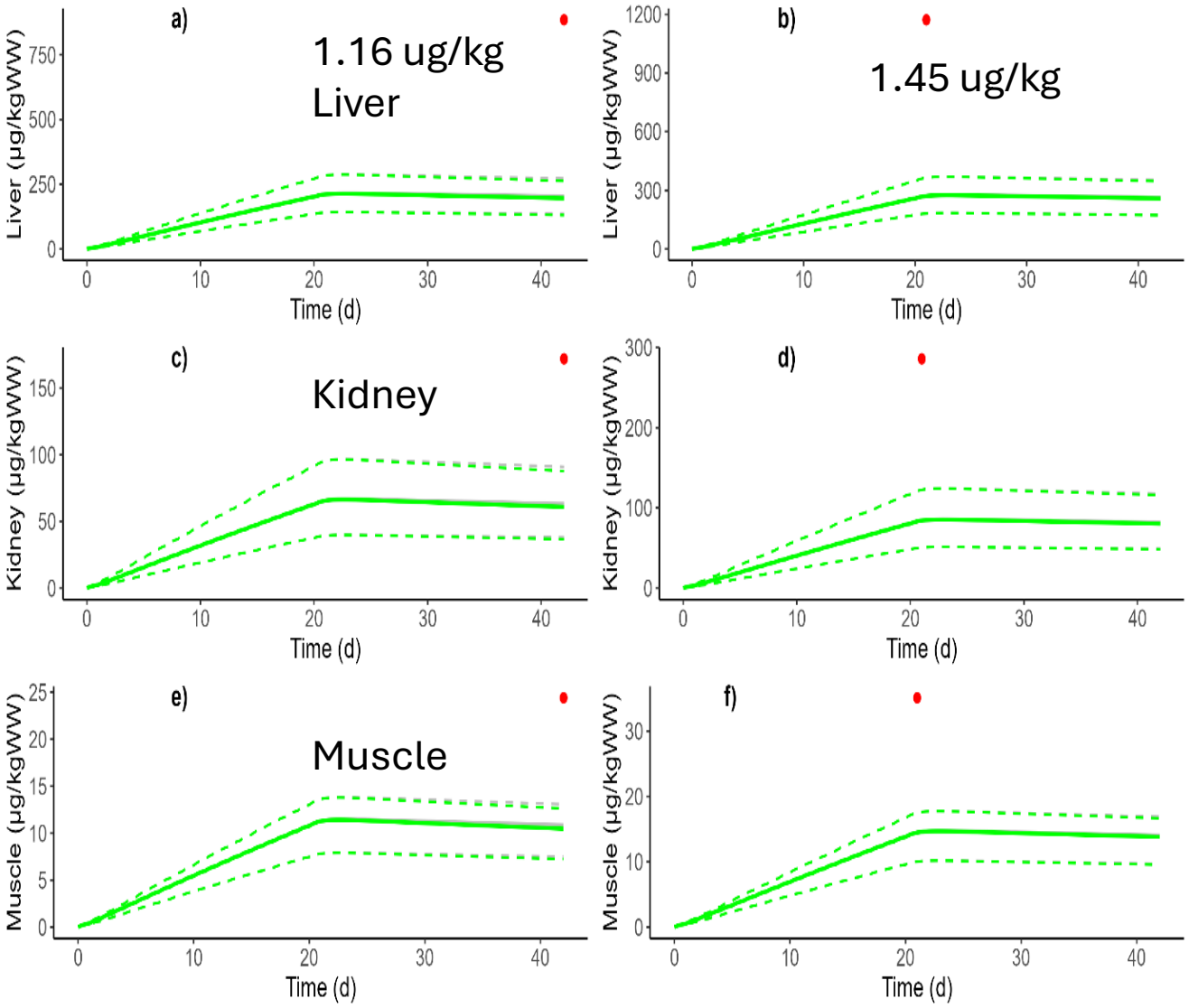
Universiteit Utrecht



Lupton et al, 2014
Lupton et al, 2015

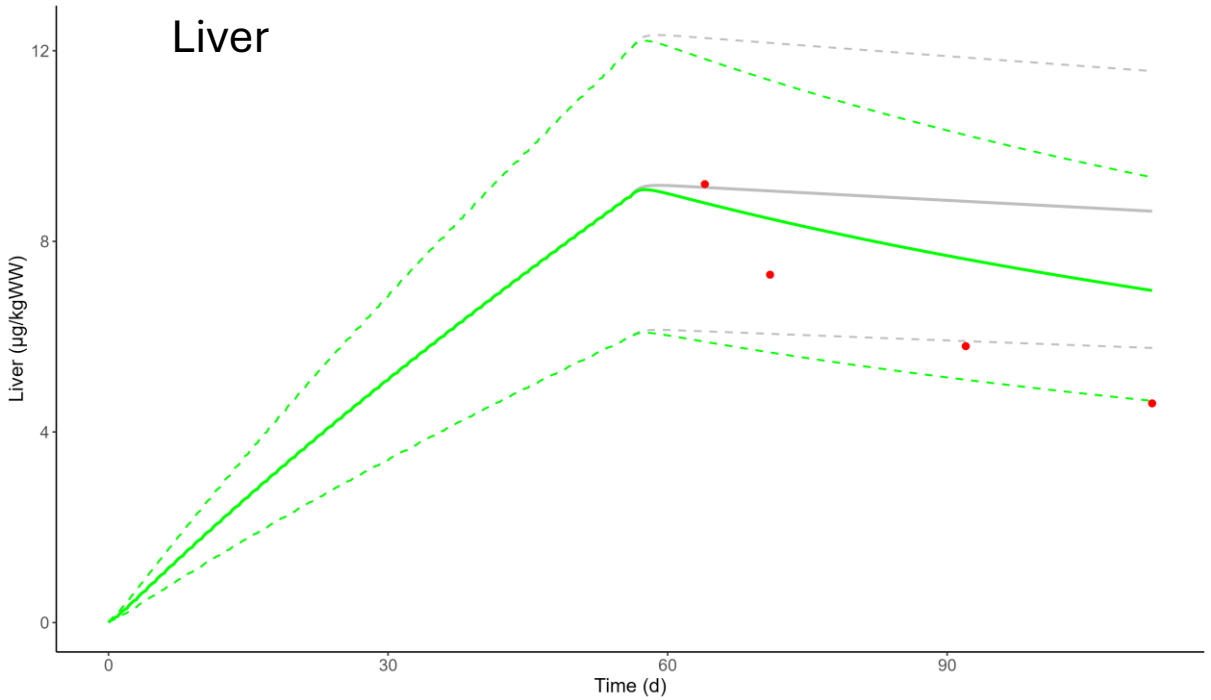
Results sheep fitting data

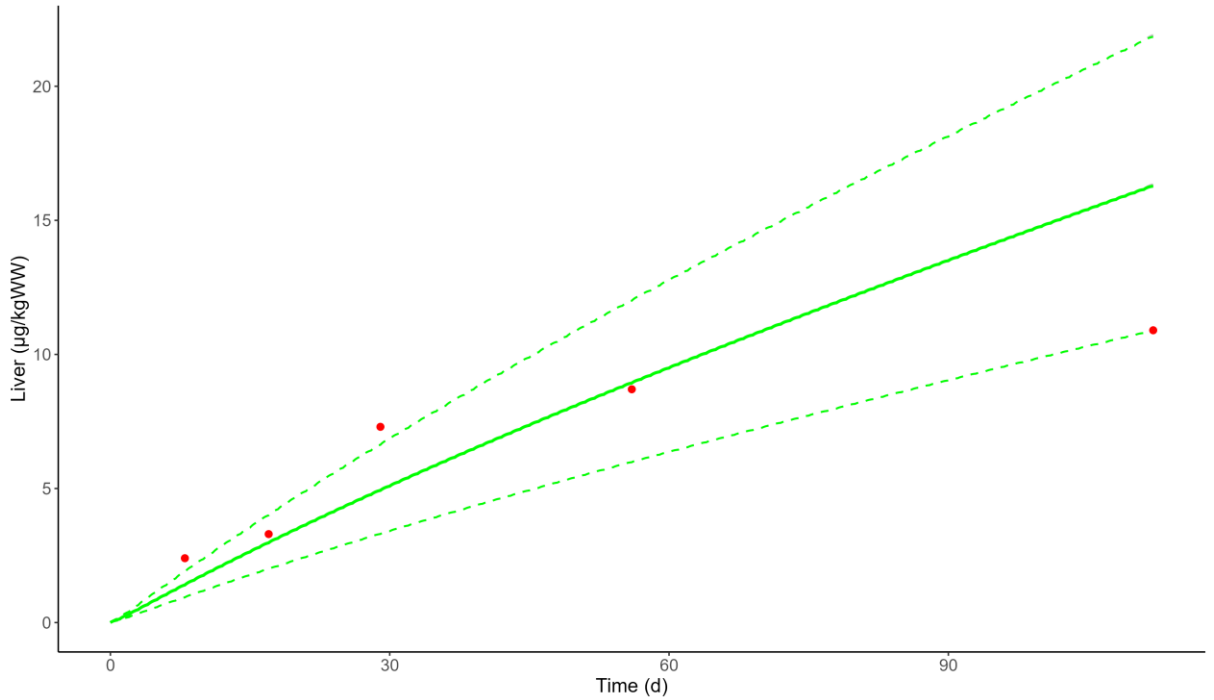




Kowalczyk et al, 2012

Results sheep liver independent data

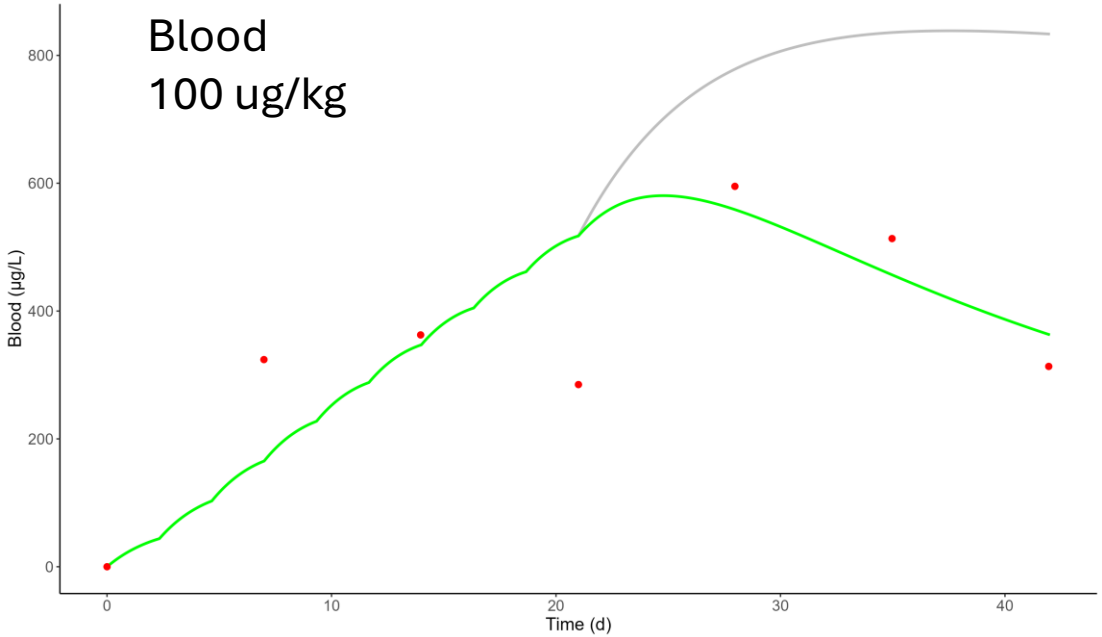


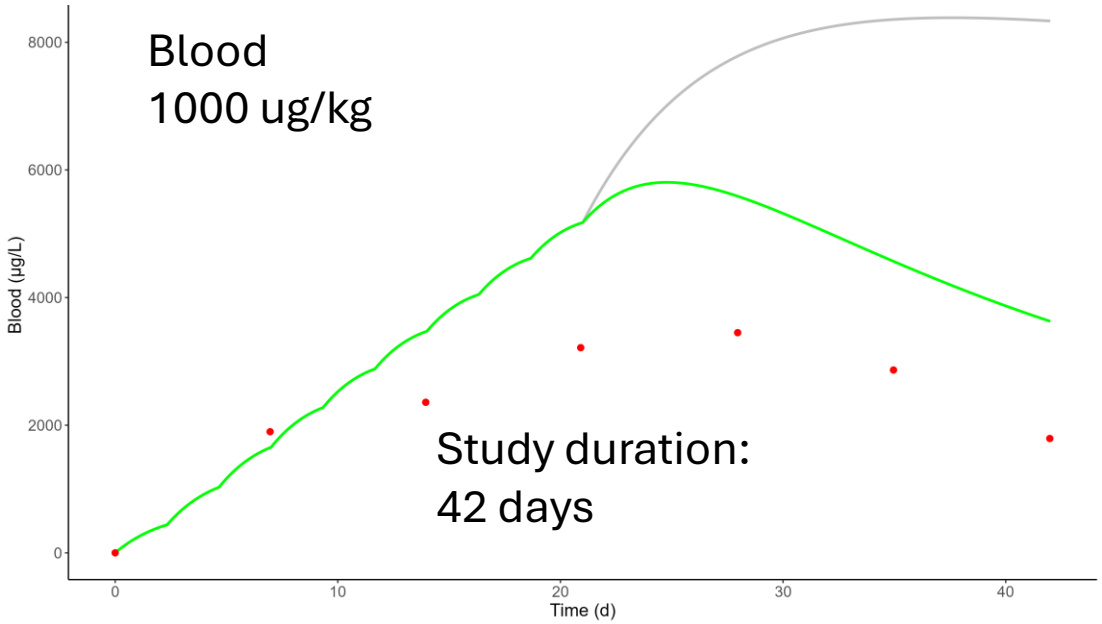


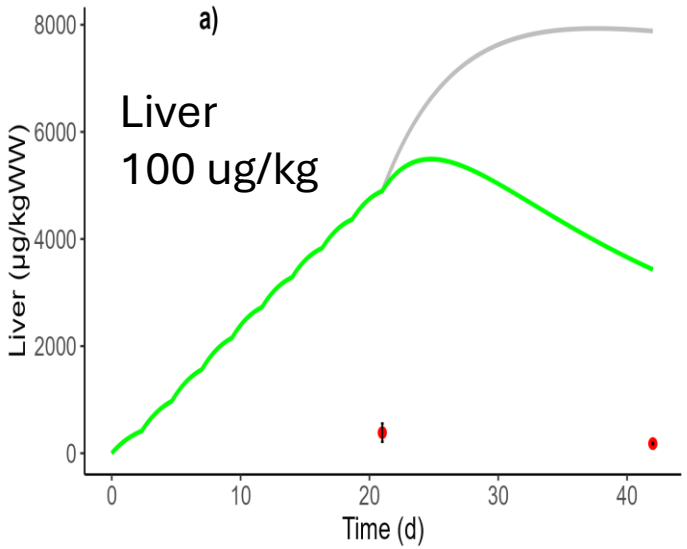
Study duration:
112 days

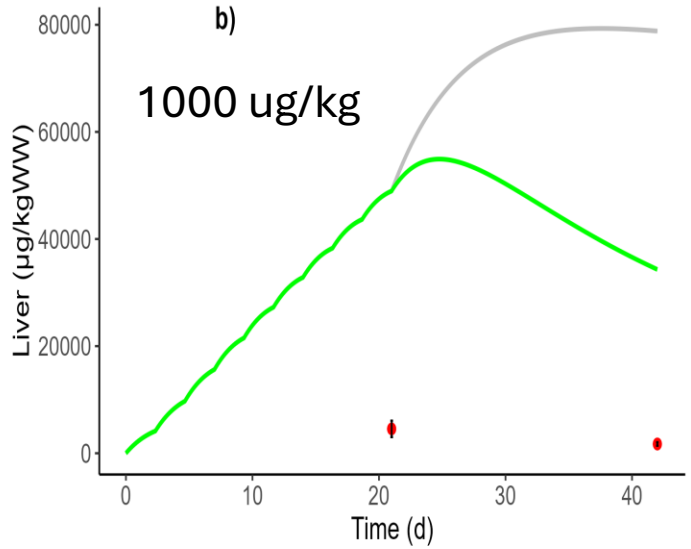
Zafeiraki et al, 2016

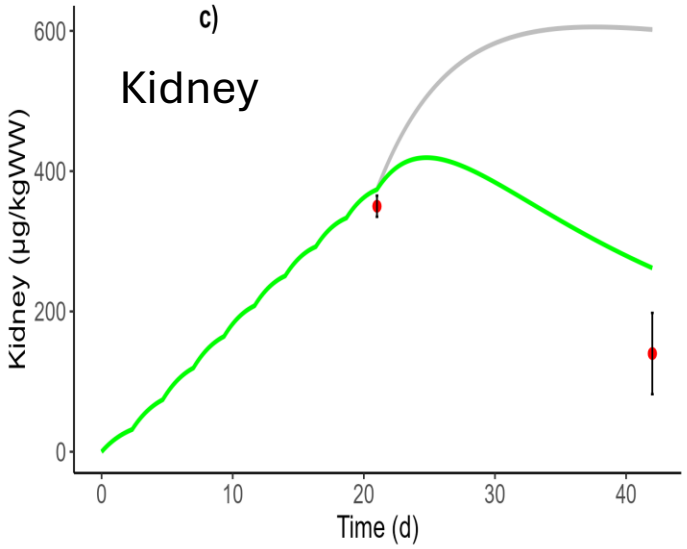
Results chicken blood and tissue

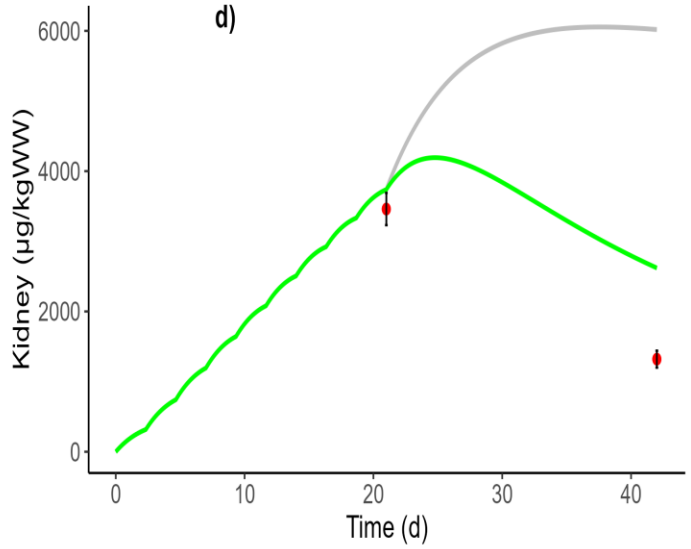












Yeung et al, 2009

Tissue prediction PFOS

Predictions of liver, kidney, muscle concentrations

- Overpredictions in beef cattle (up to 5-fold)
- Accurate or underpredictions in sheep (up to 4-fold)
- Overpredictions for liver in chicken (>10-fold)
  - Kidney predictions seem accurate

In general: concentrations liver > plasma > kidney > muscle

Partition coefficients = tissue-plasma concentration ratio

- Taken from literature

Inconsistencies literature data (chicken)

Partition coefficients

Male White Leghorn chicken

Subcutaneous implantation over 28 days

Liver-plasma concentration ratio: up to 6.5

(Yoo et al, 2009)

Evaluation study

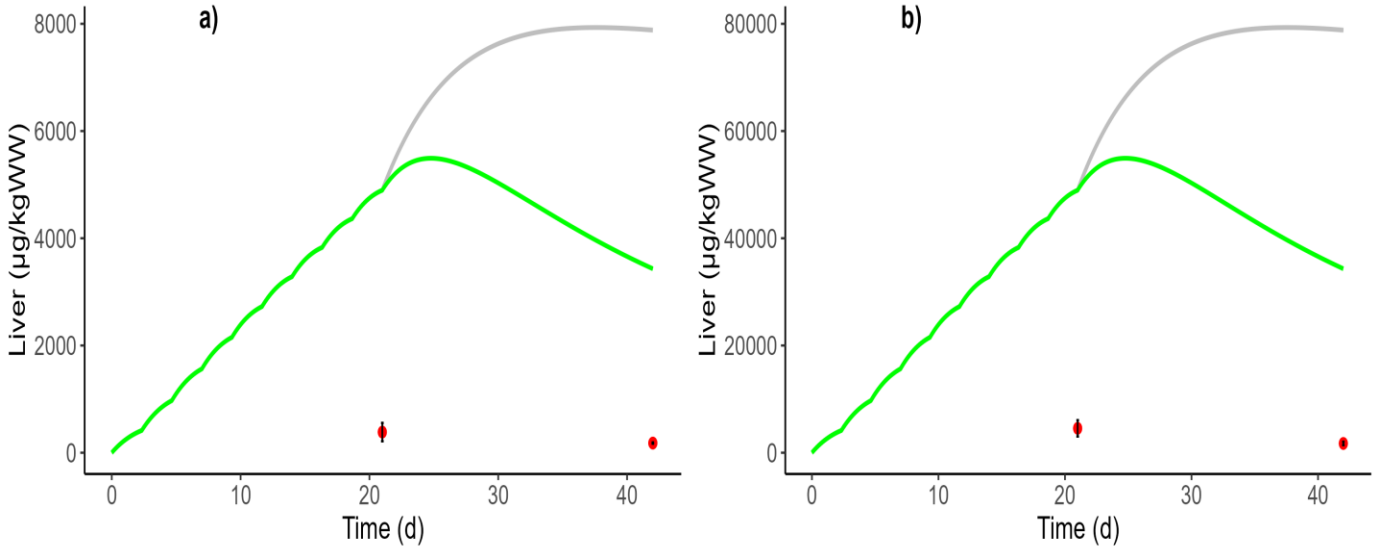
Male White Leghorn chicken

Oral administration over 21 days

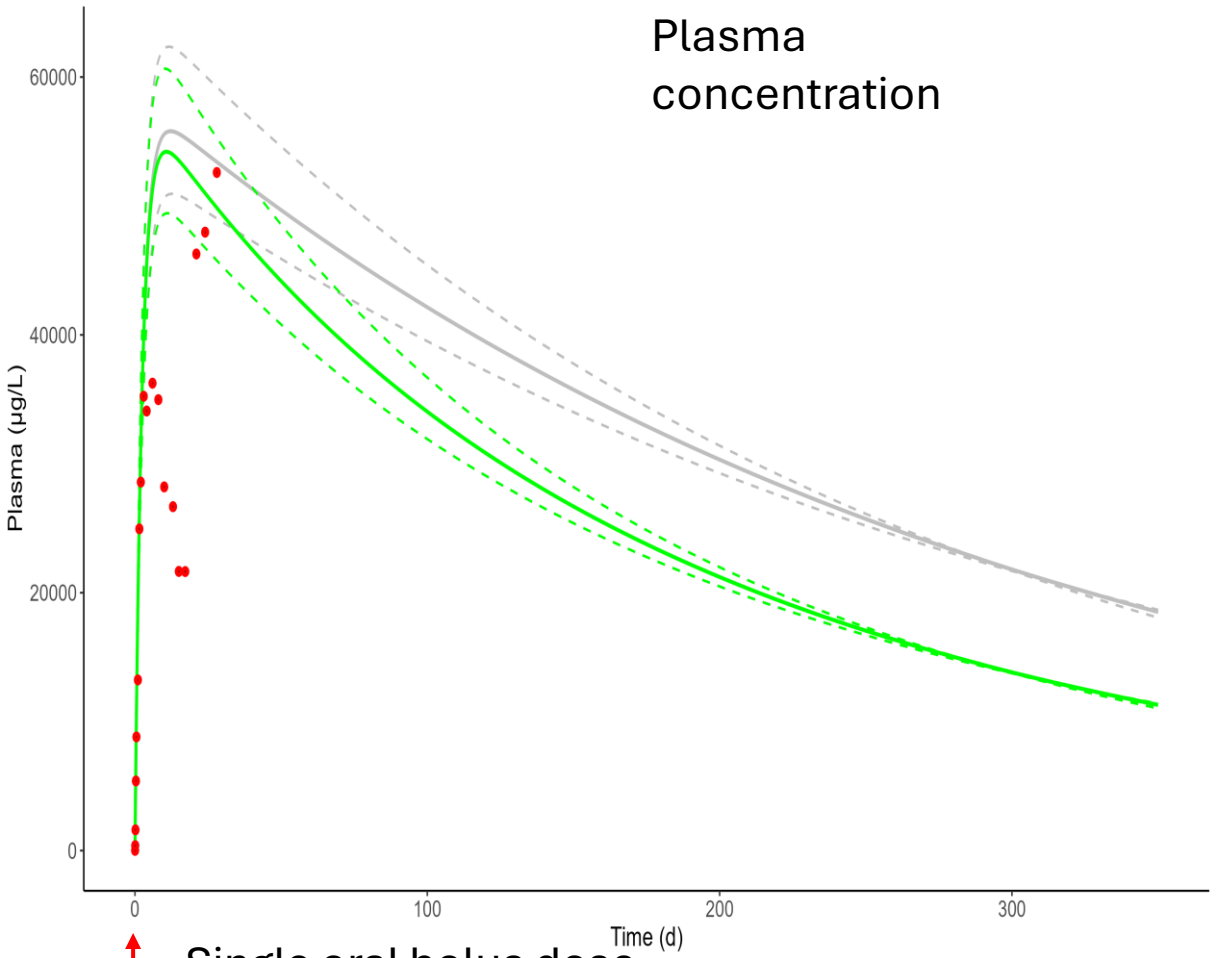
Liver-plasma concentration ratio: 0.6

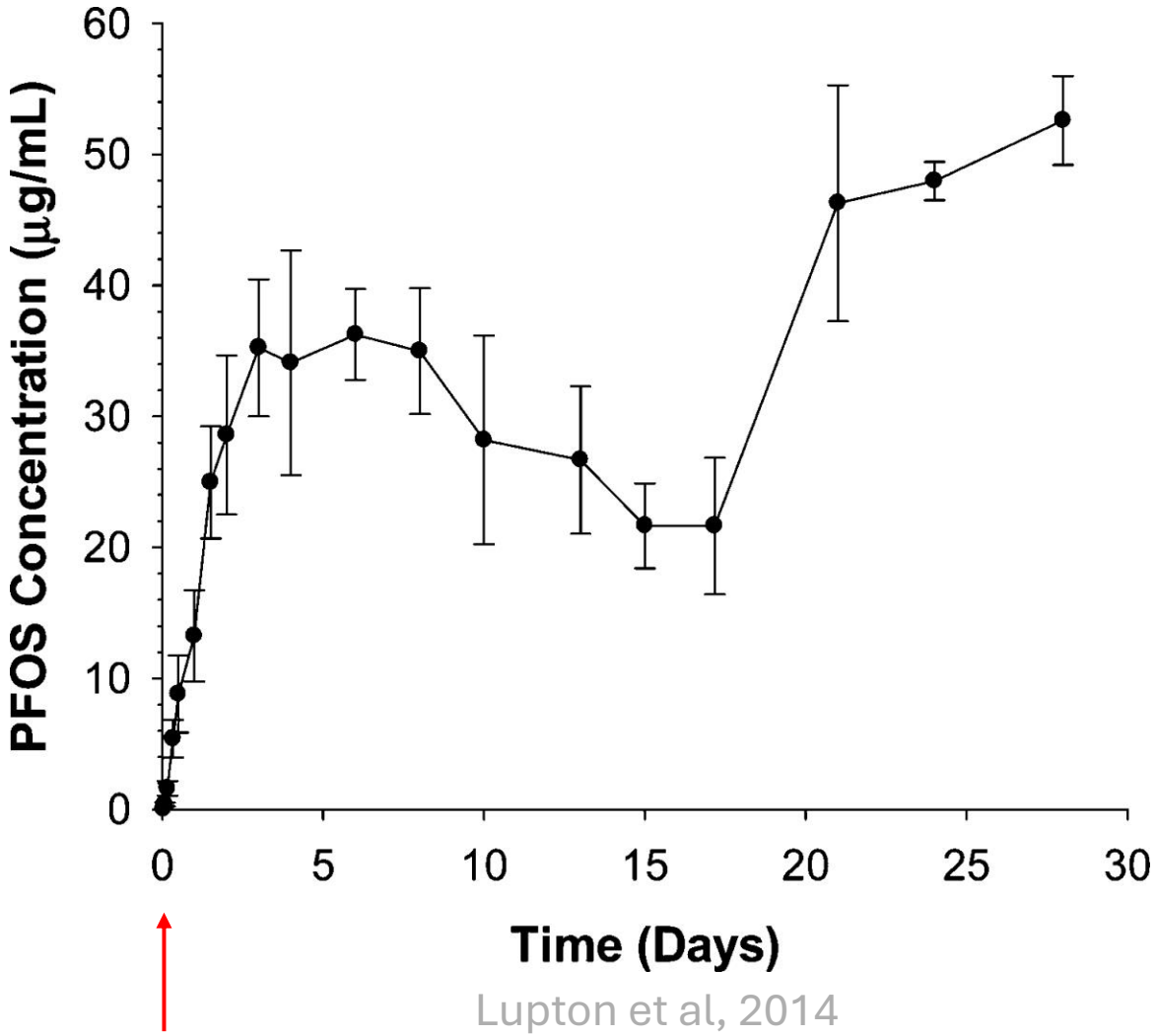
(Yeung at al, 2009)

Difference of
up to factor 10



Inconsistencies literature data (cattle)





Lupton et al, 2014

Conclusion

- Developed a PBK model including growth to predict accumulation of PFOS in livestock
- Plasma/blood predictions were accurate
- Tissue concentrations generally overpredicted

More data necessary to increase confidence in the model

Better understanding of factors influencing measurement

References

- Lupton, Sara J., Janice K. Huwe, David J. Smith, Kerry L. Dearfield, and John J. Johnston. “Distribution and Excretion of Perfluorooctane Sulfonate (PFOS) in Beef Cattle (Bos Taurus).” *Journal of Agricultural and Food Chemistry* 62, no. 5 (February 5, 2014): 1167–73. https://doi.org/10.1021/jf404355b.
- Lupton, Sara J., Kerry L. Dearfield, John J. Johnston, Sarah Wagner, and Janice K. Huwe. “Perfluorooctane Sulfonate Plasma Half-Life Determination and Long-Term Tissue Distribution in Beef Cattle (Bos Taurus).” *Journal of Agricultural and Food Chemistry* 63, no. 51 (December 30, 2015): 10988–94. https://doi.org/10.1021/acs.jafc.5b04565.
- Kowalczyk, Janine, Susan Ehlers, Peter Fürst, Helmut Schafft, and Monika Lahrssen-Wiederholt. “Transfer of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) From Contaminated Feed Into Milk and Meat of Sheep: Pilot Study.” *Archives of Environmental Contamination and Toxicology* 63 (March 28, 2012): 288–98. https://doi.org/10.1007/s00244-012-9759-2.
- Zafeiraki, Effrosyni, Irene Vassiliadou, Danae Costopoulou, Leondios Leondiadis, Helmut A. Schafft, Ron L. A. P. Hoogenboom, and Stefan P. J. van Leeuwen. “Perfluoroalkylated Substances in Edible Livers of Farm Animals, Including Depuration Behaviour in Young Sheep Fed with Contaminated Grass.” *Chemosphere* 156 (August 1, 2016): 280–85. https://doi.org/10.1016/j.chemosphere.2016.05.003.
- Yeung, Leo W. Y., Eva I. H. Loi, Vicky Y. Y. Wong, Keerthi S. Guruge, Noriko Yamanaka, Nobuhiko Tanimura, Jun Hasegawa, Nobuyoshi Yamashita, Shigeru Miyazaki, and Paul K. S. Lam. “Biochemical Responses and Accumulation Properties of Long-Chain Perfluorinated Compounds (PFOS/PFDA/PFOA) in Juvenile Chickens (Gallus Gallus).” *Archives of Environmental Contamination and Toxicology* 57, no. 2 (August 1, 2009): 377–86. https://doi.org/10.1007/s00244-008-9278-3.
- Yoo, Hoon, Keerthi S. Guruge, Noriko Yamanaka, Chihiro Sato, Osamu Mikami, Shigeru Miyazaki, Nobuyoshi Yamashita, and John P. Giesy. “Depuration Kinetics and Tissue Disposition of PFOA and PFOS in White Leghorn Chickens (*Gallus Gallus*) Administered by Subcutaneous Implantation.” *Ecotoxicology and Environmental Safety* 72, no. 1 (January 1, 2009): 26–36. https://doi.org/10.1016/j.ecoenv.2007.09.007.
- Rosato, Isabella, Tiziano Bonato, Tony Fletcher, Erich Batzella, and Cristina Canova. “Estimation of Per- and Polyfluoroalkyl Substances (PFAS) Half-Lives in Human Studies: A Systematic Review and Meta-Analysis.” *Environmental Research* 242 (February 1, 2024): 117743. https://doi.org/10.1016/j.envres.2023.117743.
- Jones, Paul D., Wenyue Hu, Wim De Coen, John L. Newsted, and John P. Giesy. “Binding of Perfluorinated Fatty Acids to Serum Proteins.” *Environmental Toxicology and Chemistry* 22, no. 11 (2003): 2639–49. https://doi.org/10.1897/02-553.
- USEPA. “Health Effects Document for Perfluorooctane Sulfonate (PFOS),” February 25, 2014. https://www.regulations.gov/document/EPA-HQ-OW-2014-0138-0003.
- Death, Clare, Cameron Bell, David Champness, Charles Milne, Suzie Reichman, and Tarah Hagen. “*Per*- and Polyfluoroalkyl Substances (PFAS) in Livestock and Game Species: A Review.” *Science of The Total Environment* 774 (June 20, 2021): 144795. https://doi.org/10.1016/j.scitotenv.2020.144795.

Acknowledgements

Funded by the TK Plate 2.0 project of the European Food Safety Authority EFSA

Special thanks to:

- Jorge Numata
- Jan-Louis Moenning
- Leonie Lautz
- Jan Hendriks
- Ronette Gehring