O204 A mechanistic physiologically-based toxicokinetic model of persistent organic pollutants transfer in growing cattle

S. Lerch [a], J. Albechaalany [a,b,c], C. Driesen [c,a], P. Schmidely [b], I. Ortigues-Marty [d], M. Zennegg [c], D. Sauvant [b], C. Loncke [b]

[a] Agroscope, Ruminants Research Group, Route de la Tioleyre 4, 1725 Posieux, Switzerland
[b] Université Paris-Saclay, INRAE, AgroParisTech, UMR Modélisation Systémique Appliquée aux Ruminants, 75005 Paris, France
[c] Empa, Laboratory for Advanced Analytical Technologies, Überlandstrasse 129, 8600 Dübendorf, Switzerland
[d] INRAE, Université Clermont Auvergne, Vetagro Sup, UMRH, 63122 Saint-Genès-Champanelle, France

Keywords: Lipophilic contaminant; Dioxins and furans; Fugacity; Risk assessment; Meat chemical safety

Introduction

Beef production occasionally faces incidents of contamination with persistent organic pollutants (POPs; e.g. dioxins/furans) that compromise consumers' confidence and induce social distress for farmers (Zennegg, 2018). Understanding and quantifying the POP absorption, distribution, metabolism and excretion (ADME) process in beef cattle is the cornerstone for handling such hazards. This remains highly challenging, as risk assessors have to cope with numerous POPs of distinct physico-chemical properties and with diverse beef farming systems (Driesen et al., 2021, 2022). The aim was to set-up a generic and integrative mechanistic model for exploring the feed-to-meat accumulation and decontamination kinetics of diverse POPs in beef cattle fed contrasting diets and following different growth rate itineraries.

Material and Methods

The physiologically-based toxicokinetic (PBTK) model describes the ADME of POPs depending on their lipophilicity (partition coefficient between octanol and water, Kow) and metabolic clearance in several types (breed, sex, diet) of growing cattle (Figure 1). Consumed pollutants flow to the intestines, where they are excreted in feces, or passively diffuse to the blood (a reverse flux back represent the blood-to-digesta non-biliary excretion). From blood, POPs are distributed between adipose tissues (first to the blood-perfused, later to the deep sub-compartment by passive diffusion; Lerch et al., 2018), muscles, liver and the rest of empty body by advection, according to their blood-perfusion rate. Metabolic clearance is represented in the liver. A model of dynamic transfer in the digestive tract is coupled to a lipid digestion model based on the INRA feeding system (2018). Distribution among tissues depends on body lipid kinetics described by the mechanistic growth model "MECSIC" (Hoch and Agabriel, 2004), including a specific development for the allocation of total body lipid mass to the six body compartments of the ADME model (Figure 1). Hepatic clearance rates were fitted for dioxin/furan congeners based on former toxicokinetic studies. Kinetics of 23478-pentachlorodibenzofuran (23478-PeCDF: moderately lipophilic: Kow $10^{7.1}$, clearance 0.65 d^{-1}) and octachlorodibenzodioxin (OCDD: highly lipophilic: Kow $10^{8.4}$, clearance 1.0 d^{-1}) were simulated for Salers heifers that grew slowly (SG; low-energy diet: 9.0 MJ ME/kg DM), fast (FG; high-energy diet: 12.5 MJ ME/kg DM), or with a compensatory growth itinerary (CG; low-energy until 500 kg and high-energy thereafter) from 314 to 700 kg BW. For each treatment, accumulation of POPs in tissues was simulated with a contaminated diet of 0.57 ng TEQ/kg DM (action level for dioxins/furans, EU regulation 277/2012). Decontamination was tested by setting the contamination level to zero after reaching 500 kg BW.

Results and Discussion

The simulated average daily gains were 0.44 in SG, and 1.14 kg/day in FG, but 0.46 until 500 kg BW and 1.34 kg/day thereafter (compensatory growth) in CG heifers. Lipid proportion in empty body increased from 11.7% at 314 kg BW, to 26.8, 28.3, and 27.7% at 700 kg for SG, FG, and CG, respectively. The 23478-PeCDF accumulation kinetics suggested that the regulatory level (2.5 pg TEQ/g lipids, EU regulation 1259/2011) would be overpassed in muscles by 3.8-fold in SG, but would only be 3-fold higher in FG and CG treatments (Figure 2A). Conversely, OCDD concentrations would remain below the regulatory level (Figure 2B). Indeed, when compared to 23478-PeCDF, the higher lipophilicity of OCDD lowered its absorption rate (Driesen et al., 2022). The decontamination half-life for 23478-PeCDF was lowered by compensatory growth (116 days in CG heifer), when compared to continuous SG (178 days) and FG (126 days). This resulted, at least in

Figure 1. Conceptual diagram of the physiologically-based toxicokinetic (PBTK) model describing the fate of persistent organic pollutants in growing cattle.

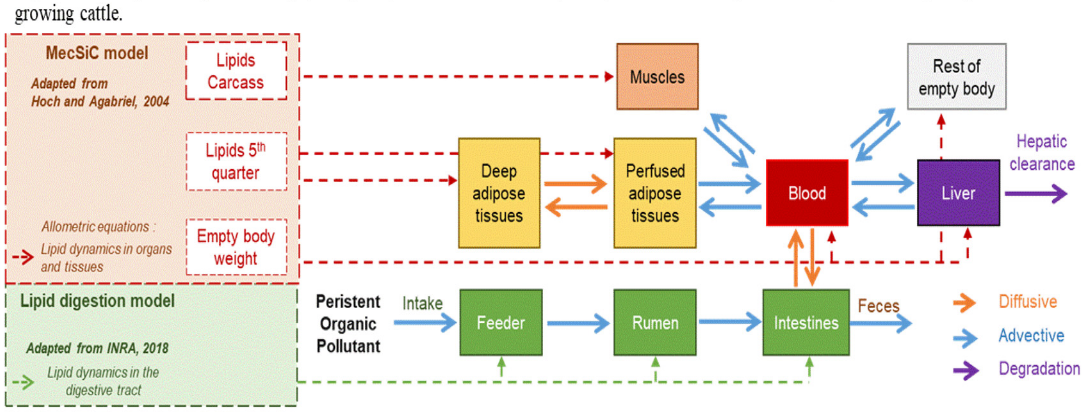
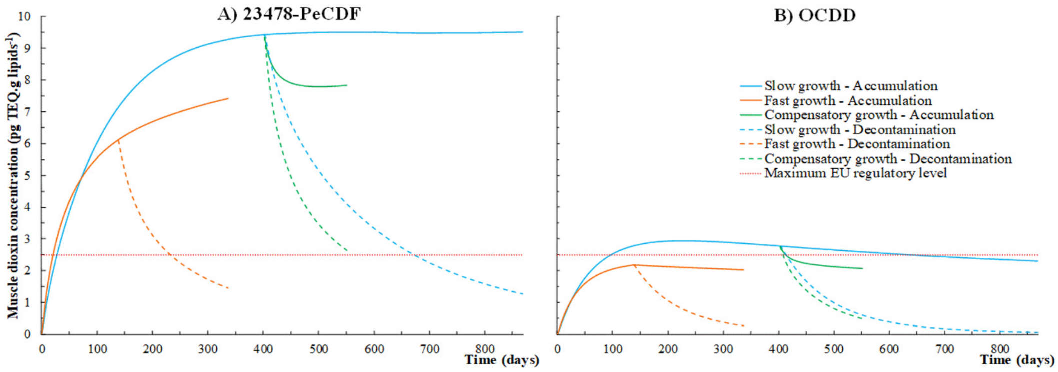


Figure 2. Accumulation and decontamination kinetics of 23478-PeCDF (A) and OCDD (B) concentrations in muscles of Salers heifers, receiving low-energy diet (slow growth), high-energy diet (fast growth), or with a compensatory growth itinerary (compensatory growth) from 314 to 700 kg BW. Diet 23478-PeCDF or OCDD contamination level of 0.57 ng TEQ/kg DM was applied for the accumulation phase and set to zero after 500 kg BW for the decontamination period.



part, from a typical dilution effect during decontamination, due to a higher rate of body lipids deposited in CG (0.59 kg/day) than in FG (0.41 kg/day) and SG (0.18 kg/day), in line with previous *in vivo* findings (Driesen et al., 2021).

Conclusion and Implications

The use of a mechanistic PBTK model highlighted the complex interplay between POPs' physico-chemical properties and beef cattle lipid kinetics on feed-to-meat accumulation and decontamination rates. Further developments are ongoing to deliver a decision-making tool for risk assessors and managers, and ultimately contribute to beef meat chemical safety.

References

C.Driesen, S.Lerch, R.Siegenthaler, P.Silacci, H.D.Hess, B.Nowack, M.Zennegg, 2022. Accumulation and decontamination kinetics of PCBs and PCDD/Fs from grass silage and soil in a transgenerational cow-calf setting. Chemosphere 296.

C.Driesen, M.Zennegg, I.Morel, H.D.Hess, B.Nowack, S.Lerch, 2021. Average transfer factors are not enough: The influence of growing cattle physiology on the transfer rate of polychlorinated biphenyls from feed to adipose. Chemosphere 270.

T.Hoch, J.Agabriel, 2004. A mechanistic dynamic model to estimate beef cattle growth and body composition. 1. Model description. Agricultural Systems 81, 1–15.

INRA, 2018. INRA feeding system for ruminants. Wageningen Academic Publisher, p. 640.

S.Lerch, O.Martin, A.Fournier, J.Henri, 2018. Exploring the effects of dietary lipid content and digestibility on lipophilic contaminants transfer from feed to milk in dairy cow: insights from a physiologically-based toxicokinetic modelling approach. Advances in Animal Biosciences 9, 444.

M.Zennegg, 2018. Dioxins and PCBs in Meat - Still a Matter of Concern?. Chimia 72, 690–696.

doi: 10.1016/j.anscip.2022.07.214

O205 The perturbation vector: a new integrative approach for assessing the individual metabolic resilience of dairy cows

E. Jorge-Smeding [a,b], A. Kenez [b], A. Álvarez-Oxiley [a], L. Astigarraga [a], A.I. Trujillo [c], A.L. Astessiano [c]

[a] DPAP, Facultad de Agronomía, Universidad de la República, Montevideo, Uruguay
[b] Department of Infectious Diseases and Public Health, City University of Hong Kong, Hong Kong, China
[c] DPAP, Facultad de Agronomía, Universidad de la República, Montevideo, China

Keywords: Resilience; Physiology; Metabolic adaptions

Introduction

The main metabolic responses of the dairy cow during the transition period are well established, however there is still needed the development of mathematical approaches for assessing the metabolic trajectory in an integrated manner.

We propose the use of a new mathematical approach called perturbation vector (Pv), which summarizes all metabolic features at any given time of an experiment on the basis of the concentrations fold change of each metabolite/hormone. The objective was to evaluate the use of Pv as a dynamic measure of metabolic perturbations on the mid-term time scale (lactation cycle) in a low-input pastoral system with two breeds expected to have contrasting adaptative capacity (Normande, NR; Holstein Friesian, HF). Additionally, we aimed to assess the use of the 1st harmonic model (cyclic model) to further derive new variables featuring the individual metabolic resilience.

Material and Methods

Metabolic data comprising several metabolites/hormones commonly (non-esterified fatty acids, β-hydroxybutyrate, cholesterol, glucose, insulin, urea, total protein and albumin) measured monthly in 27 multiparous cows (HF, n = 14; NR, n = 13) along between -15 and 340 days in milk (DIM) was used. The Pv was calculated for each cow at each given time as follows: $\sqrt{(\sum xi2)}$, where xi denotes the concentration fold-change of each metabolite after log-normalization over the median. Pv = 0 was assumed to reflect non-perturbated states, while greater values were indicative of increased perturbation levels. The results were analyzed as repeated measures considering the