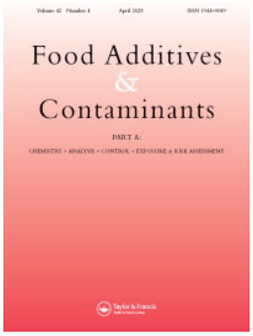

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Congener-specific transfer modelling of dioxins and dioxin-like PCBs in free-ranging cattle grazing in the Dutch floodplains

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ABSTRACT

Cattle grazing in the Dutch floodplains are exposed to polychlorinated dibenzo-p-dioxins and dibenzofurans (dioxins) and dioxin-like PCBs (dl-PCBs) through the consumption of grass and adhering soil. This can lead to elevated dioxin and dl-PCB levels in meat fat. To manage this contamination issue, the kinetics of these compounds in cattle need to be better understood. This study describes the development and application of a physiologically based kinetic (PBK) model to predict dioxin and dl-PCB levels in muscle fat of 'Rode Geus' cattle based on measured levels in grass and soil. Calibration of the model was performed separately for each congener, using measured dioxin and dl-PCB levels in various tissues of 14 animals. Model validation performed using dioxin and dl-PCB samples of 14 other cattle, showed that PBK model predictions were on average a factor 2.4 higher than the measured dioxin and dl-PCB TEQ levels in fat. Despite this difference, the model may still be particularly useful to better understand the relation between environmental dioxin and dl-PCB levels and those in cattle. The model is publicly available with a user-friendly interface on www.feedfoodtransfer.nl and may provide relevant insights for risk assessment and risk management.

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Dioxins and dl-PCBs; PBK modelling; floodplains; free-ranging cattle

Introduction

Free-ranging cattle graze year-round in the floodplains between dykes and rivers in the Netherlands as part of vegetation control and nature management. The cattle include various breeds, such as Rode Geus, Galloway, Tauros, and Scottish Highlanders, which are resilient to harsh weather conditions and require little care-taking (BuRO 2022). To ensure that the size and composition of the herd remains constant, surplus animals are occasionally slaughtered and their meat is ideally sold for human consumption. However, it has been recently observed that muscle fat and the liver of free-ranging cattle in several floodplains in the Netherlands contain elevated levels of polychlorinated dibenzo-p-dioxins and dibenzofurans (dioxins) and dioxin-like PCBs (dl-PCBs). In fact, dioxin and dl-PCB levels exceeded the EU maximum levels (MLs) (Commission Regulation 2023) in over 70% of the samples taken from free-ranging cattle grazing in the floodplains year-round (BuRO 2022; Hoogenboom et al. 2022b).

Dioxins and dl-PCBs are persistent environmental contaminants that can accumulate in food-producing animals and humans. Animal derived food is considered a major source for background exposure humans. Exposure to dioxins and dl-PCBs of concern may cause several adverse effects, including decreased sperm concentrations in men exposed at a young age (EFSA Panel on Contaminants in the Food Chain 2018). The presence of dioxins and dl-PCBs in animal products is often linked to the presence of these chemicals in animal feed (Malisch and Kotz 2014). In case of the free-ranging cattle, contamination likely stems from consumption of grass and adhering soil (Hoogenboom et al.

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2022a, 2022b). In particular, levels in soil of the floodplains are higher than levels observed in regular pastures, due to deposition of contaminated sediment after flooding of the floodplains.

To manage the contamination issue, it is important to understand the kinetics of these compounds in cattle and predict the levels in muscle fat during different seasons. Concentrations in milk are of lesser importance since the milk of these free-ranging cows is not used for human consumption. In addition, the relationship between dioxin and dl-PCB concentrations in bovine products and the seasonal variation in measured levels in soil and grass, as well as the effect of moving animals to a cleaner environment, need to be better understood.

To this end, a method that is particularly useful is physiologically based kinetic (PBK) modelling. A PBK model comprises multiple compartments that represent physiologically relevant tissues. This enables the simulation of substance distribution throughout the body and allows for the estimation of its concentration in various tissues over time. The overall mixture concentration of dioxins and dl-PCBs in human food products is typically expressed as toxic equivalents (TEQ) of the reference chemical using the toxic potencies, i.e. Toxic Equivalency Factors (TEF-values), of the congeners in the mixture (Van den Berg et al. 2006; DeVito et al. 2024). With the model, it is ideally possible to estimate whether dioxin and dl-PCB TEQ levels in beef exceed regulatory limits, before slaughtering the animals.

As identified in a review article (Lautz et al. 2019), two PBK models have been developed to estimate the distribution and accumulation of dioxins and dl-PCBs in cattle (Derks et al. 1994; Freijer et al. 1999; Hoogenboom et al. 2010). Furthermore, Bogdal et al. (2017) published a PBK model based on the model reported by Derks et al. (1994). These published PBK models solely focused on the TEQ kinetics, i.e. concentrations of the various congeners in feed are first translated into a TEQ concentration before the corresponding TEQ concentration in the compartment of interest (here muscle fat as a proxy for beef concentrations) is calculated using a PBK model. Hence, the PBK model only contains TEQ-specific kinetic parameter values. In this paper, we will refer to this approach as the total-TEQ approach. However, it has been shown that large differences can be expected between the kinetic properties of dioxin and dl-PCB congeners (EFSA Panel on Contaminants in the Food Chain 2018; Driesen et al. 2022; Savvateeva et al. 2022; Notenboom et al. 2023), which may lead to less accurate estimates of TEQ concentrations in bovine food products.

More recently, studies have been published that focused on congener-specific bovine models (Krause et al. 2023; Moenning, Krause, et al. 2023; Moenning, Lamp, et al. 2023), where the concentration of each individual congener is estimated in the PBK model's compartments using congener-specific kinetics. In contrast to the total-TEQ approach, the TEQ concentration is estimated after applying the (congener-specific) PBK model. These congener-specific approaches have been developed to estimate the transfer of dioxins and dl-PCBs to milk fat of dairy.

However, these congener-specific bovine models were specifically developed for dairy cattle, which may differ from sturdy cattle grazing in the floodplains. Differences in physiology and kinetics have been reported, such as total body weight, growth rates, relative compartment weights, and milk production (Adriaens et al. 2023; Albechaalany et al. 2024). In addition, these models do not account for growth of animals, which means that they cannot be used for typical herds consisting of animals of various ages. As such, a PBK model to estimate the transfer of dioxins and dl-PCBs to beef of free-ranging cattle grazing in the floodplains is still lacking.

The present study therefore aimed to develop a new PBK model to estimate the TEQ concentration in muscle fat of cattle grazing in floodplains. Kinetics were modelled using both the total-TEQ approach and the congener-specific approach. The developed model is specific to the so-called 'Rode Geus', which is a breed that is commonly found on the Dutch floodplains. Furthermore, growth of the animals and seasonal changes in feed consumption and grass levels are incorporated. The developed model is validated with measured kidney fat levels, which are representative of muscle fat levels, from cattle that had been grazing in two Dutch floodplains, both along the Waal River. The model is publicly

available (www.feedfoodtransfer.nl) and can be used to estimate individual TEQ levels in muscle fat of free-ranging Rode Geus cattle.

Materials and methods

PBK model structure

The chosen PBK model structure was inspired by the model developed by Derks et al. (1994) for the dairy cow and was modified to describe the situation for Rode Geus cattle grazing in the floodplains. A detailed description of the model structure is also provided by Minnema et al. (2024).

The overall structure of the PBK model developed in the present study is presented in Figure 1. The model consists of five compartments, specifically, the liver, richly perfused organs, poorly perfused organs, fat, and blood. Slowly perfused organs are purported to include the skin, subcutaneous tissue, and muscle, whereas richly perfused organs are purported to include e.g. heart, lungs, kidneys, spleen, and brain. The exposure to dioxins and dl-PCBs is modelled as the oral consumption of contaminated grass and adhering soil. To mimic ingestion, an absorption fraction is applied which represents the amounts of dioxins and dl-PCBs that are absorbed into the body. Once absorbed, the dioxins and dl-PCBs directly enter the liver compartment. This represents the biological process in which dioxins and dl-PCBs that are absorbed *via* the gastro-intestinal (GI-)tract are transported to the liver *via* the hepatic portal vein. This process was modelled similarly in previous PBK models (Derks et al. 1994; Traag et al. 2006; Hoogenboom et al. 2010).

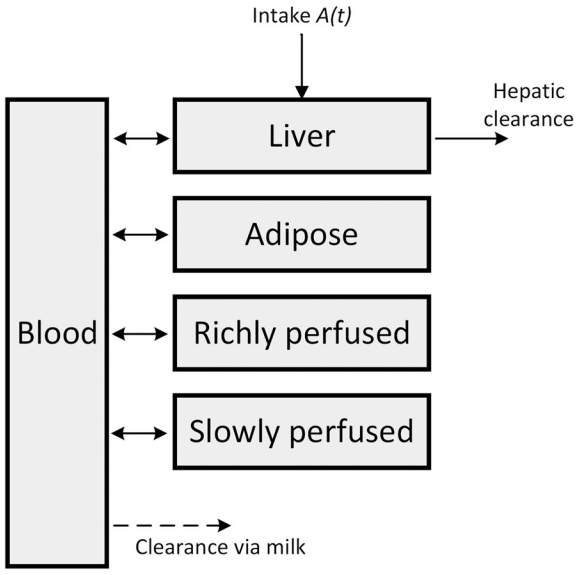

Figure 1. Schematic overview of the PBK model implemented in this study. Note that compartment sizes are sex and age specific. Clearance *via* milk is only modelled for cows older than 2 years during the lactation period (April 1st–September 30th).

After entering the liver, dioxins, and dl-PCBs can be eliminated through hepatic clearance or migrate to the blood compartment. Once dioxins and dl-PCBs circulate through the body *via* the systemic blood, they are distributed to the remaining compartments (i.e. poorly perfused organs, richly perfused organs, and adipose tissue).

For cows, dioxins and dl-PCBs that reside in the blood compartment can also be excreted *via* milk. It is assumed that cows calve after they reach an age of two years. The lactation period that accompanies a calving is assumed to take place in the spring and summer period (April 1st–September 30th). During the lactation period, cows also have an increased cardiac output (Supplemental Materials; Table S3), which was taken into account in the model. It is assumed that the cows calve every year.

Growth is incorporated in the model and the relative size of the compartments are scaled to the total body weight. The total body weight was modelled by fitting Brody's equation (Brody and Lardy 1946) to measured body weights of cattle grazing in the floodplains (Supplemental Materials; Table S1). The parameters were fitted separately for cows and bulls. The resulting parameters can be found in the Supplemental Materials (Section 1.1) and the resulting growth curves are shown in Figure S1. Relative compartment sizes with respect to the body weight without gastro-intestinal content (Tables S2), were assumed to be the same for cows and bulls and to remain constant during the lifetime of the cattle. An exception to this was the adipose compartment and the slowly perfused organs compartment, which differed between cows and bulls. Since the seasonal variations in the exposure of dioxins and dl-PCBs *via* grass are considered in this work, we also incorporated the date of birth.

Keeping the abovementioned considerations in mind, the PBK model is described by the following set of differential equations.

$$\frac{dA_{blood}(t)}{dt} = \rho \times \left(\begin{array}{l} -\frac{Q_{adipose}}{F_q} \times \left(c_{blood}(t) - \frac{c_{adipose}(t)}{p_{fat}} \right) \\ - Q_{slowly\ perfused} \times \left(c_{blood}(t) - \frac{c_{slowly\ perfused}(t)}{p_{slowly\ perfused}} \right) \\ - Q_{richly\ perfused} \times \left(c_{blood}(t) - \frac{c_{richly\ perfused}(t)}{p_{richly\ perfused}} \right) \\ - Q_{liver} \times \left(c_{blood} - \frac{c_{liver}(t)}{p_{liver}} \right) - cl_m \times c_{blood}(t) \end{array} \right) \quad (1)$$

$$\frac{dA_{adipose}(t)}{dt} = \rho \times \left(\frac{Q_{adipose}}{F_q} \times \left(c_{blood}(t) - \frac{c_{adipose}(t)}{p_{adipose}} \right) \right) \quad (2)$$

$$\frac{dA_{slowly\ perfused}(t)}{dt} = \rho \times \left(Q_{slowly\ perfused} \times \left(c_{blood}(t) - \frac{c_{slowly\ perfused}(t)}{p_{slowly\ perfused}} \right) \right) \quad (3)$$

$$\frac{dA_{richly\ perfused}(t)}{dt} = \rho \times \left(Q_{richly\ perfused} \times \left(c_{blood}(t) - \frac{c_{richly\ perfused}(t)}{p_{richly\ perfused}} \right) \right) \quad (4)$$

$$\frac{dA_{liver}(t)}{dt} = \rho \times \left(Q_{liver} \times \left(c_{blood}(t) - \frac{c_{liver}(t)}{p_{liver}} \right) - cl_l \times \frac{c_{liver}(t)}{p_{liver}} \right) \quad (5)$$

$$\frac{dA_{milk}(t)}{dt} = \rho \times \left(cl_m \times c_{blood}(t) \right) \quad (6)$$

Here, $A_i(t)$ represents the amount [ng] of a congener in compartment i at time t, $c_i(t)$ represents the concentration [ng/kg] of a congener in compartment i at time t, and cl_m represents the clearance [L/day] of the congener due to excretion to milk (0 L/day for bulls), and cl_l represents the hepatic clearance [L/day]. F_q [-] is the diffusion limiting flow factor in the adipose tissue, p_i [-] is the partition coefficient between compartment i and blood, and Q_i [L/day] is the perfusion to compartment i. Parameter ρ represents the tissue density [kg/L], which is assumed to be 1 kg/L for all tissues in the model. The hepatic clearance, cl_l, [L/day] is calculated as follows:

$$cl_l = kMet \times V_l \quad (7)$$

where $kMet$ [day^{-1}] is the metabolic rate constant and V_l is the liver volume [L].

Further details on the underlying parameter values and model assumptions are given in the Supplemental Materials.

The calculation of the dioxin and dl-PCB concentrations in muscle fat was performed as follows:

$$C_{muscle\ fat} = \frac{C_{slowly\ perfused} \times p_{adipose}}{p_{slowly\ perfused} \times v_{fat}} \quad (8)$$

with $C_{muscle\ fat}$ being the congener concentration in muscle fat, $c_{slowly\ perfused}$ being the congener concentration in the slowly perfused organ compartment, $p_{adipose}$ being the adipose: blood partition coefficient, $p_{slowly\ perfused}$ being the slowly perfused tissue: blood partition coefficient, and v_{fat} being the fraction of fat cells in adipose tissue. Here, it is assumed that v_{fat} is 0.8 (Thomas 1962). A full explanation and derivation of Equation 8 is provided in Minnema et al. (2024).

In this study, dioxin and dl-PCB concentrations in blood fat were used during model calibration (see below). To estimate the concentration in blood fat, it was assumed that all dioxins and dl-PCBs in blood accumulate in the fatty particles comprising 0.21% of the total blood volume. This is based on the measurements of Yamdagni and Schultz (1970), who estimated that the total fraction of fatty cells in plasma is ~0.42%. Assuming 50% plasma, this equals 0.21% of fatty particles in blood. This leads to the following equation to estimate dioxin and dl-PCB concentrations in blood fat:

$$C_{blood\ fat} = \frac{C_{blood}}{0.0021} \quad (9)$$

Modelling of dioxin and dl-PCB exposure

Since this study is not a controlled trial, the exact exposure of the animals is unknown. To model the distribution and accumulation of dioxins and dl-PCBs, exposure scenarios needed to be defined that can serve as an input for the PBK model. The amount of dioxins and dl-PCBs that is absorbed, $A_{in}(t)$, was modelled as follows:

$$A_{in}(t) = A_{grass}(t) \times c_{grass}(t) \times f_{grass} + A_{soil}(t) \times c_{soil}(t) \times f_{soil} \quad (10)$$

with A_{grass} [kg] and A_{soil} [kg] denoting the amount of grass and adhering soil that is eaten, respectively. $c_{grass}(t)$ [ng/kg] and $c_{soil}(t)$ [ng/kg] represent the dioxin and dl-PCB concentrations in grass and soil. Finally, f_{grass} and f_{soil} [–] are the absorption fraction of dioxins and dl-PCBs from grass and soil.

In the present study, the absorption fractions were calibrated for each individual congener. Since it is impossible to fit separate absorption fractions for grass and soil with the available data, it was assumed that the same absorption fraction (f_{abs}) can be used for both grass and soil, i.e. $f_{abs} = f_{grass} = f_{soil}$.

The exposure *via* milk of calves younger than 6 months was modelled as follows:

$$A_{in}(t) = A_{milk}(t) \times c_{milk}(t) \times f_{milk} \quad (11)$$

with $c_{milk}(t)$ denoting the dioxin and dl-PCB concentration in milk and f_{milk} denoting the absorption of dioxins and dl-PCBs through milk. Although the model supports exposure to dioxins and dl-PCBs through milk, $c_{milk}(t)$ was set at 0 ng/L in this study, due to a lack of empirical data on possible concentrations in milk.

Exposure via grass, soil, and milk

In the modelling presented in this study, it was assumed that cattle start eating grass and adhering soil from the age of 6 months. Specifically, it is assumed that the consumption of dry matter (d.m.) grass is equal to 2% of the body weight of the cattle. Although lactating cows may eat slightly more than 2% of their body weight (i.e. ~3%) (Aroeira et al. 1999; Méndez et al. 2020), the modelled consumption of 2% d.m. grass is generally consistent between various types of cattle and types of grass (Gwayumba et al. 2002; Estrada et al. 2004). The amount of adhering soil that is consumed by cattle during grazing, is modelled as a percentage of the amount of grass that is eaten, which differs between summer and winter. In summer, grass is longer, which means that the amount of adhering soil taken in by cattle is expected to be lower than in winter when grass is shorter. In summer, the amount of adhering soil (d.m.) taken in by cattle is assumed to be 4% of the amount of grass (d.m.) that is eaten whereas the percentage of adhering soil in the winter is assumed to be 8%. These fractions are in line with data published by Jurjanz et al. (2012).

For cattle younger than 6 months, the only source of dioxins and dl-PCBs is assumed to be milk. The amount of milk that is consumed by the young cattle per day is assumed to be higher than the amount of grass that is eaten, i.e. 10% of the total body weight. Note that since the dioxin and dl-PCB concentrations in milk were set to 0 ng/L in this study, the amount of consumed milk will not affect the results here. Furthermore, it must be noted that placental transfer of dioxins and dl-PCBs was not considered in this model. Placental transfer was shown to be relevant in the first weeks after birth for non-dioxin-like PCBs (ndl-PCBs) (Moenning, Numata, et al. 2023) and may be a relevant process for dioxins and dl-PCBs as well. Nevertheless, after a couple of months after birth, the impact of placental transfer is negligible compared to exposure *via* milk.

Dioxin and dl-PCB concentrations in grass, soil, and milk

The dioxin and dl-PCB concentrations in grass vary during the year. They tend to be lower in the spring and summer than in the fall and winter, due to the growth of grass (Traag et al. 2006). To account for this growth, the levels in grass over time are calculated as follows:

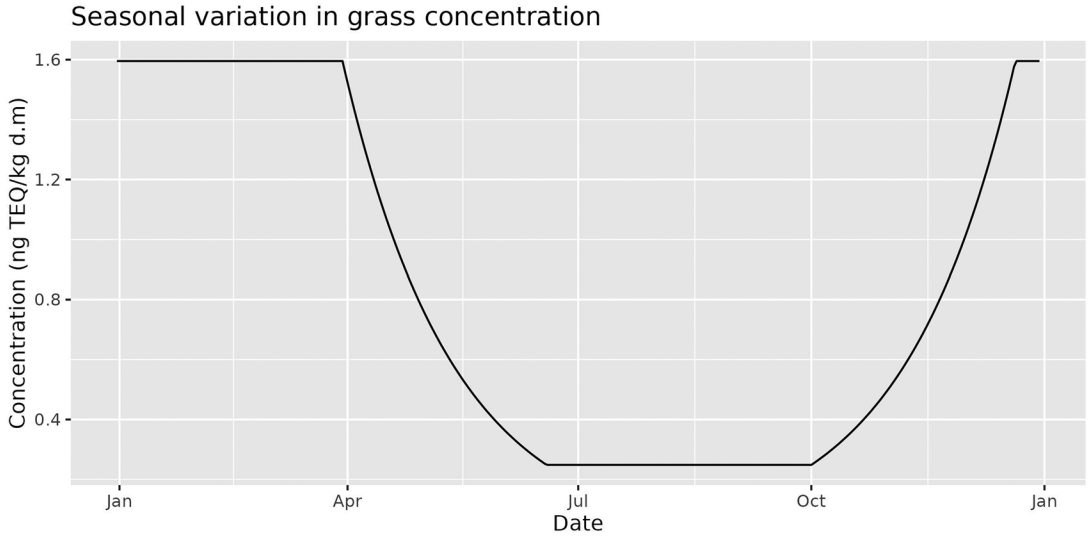

Figure 2. Example of the seasonal variation in the grass concentration. In this example, a maximum grass concentration ($c_{grass,\,max}$) of 1.6 ng/kg grass (d.m.) was used, whereas a minimum concentration ($c_{grass,\,min}$) of 0.3 ng/kg grass was used. At the start of spring (April 1st), grass concentrations start to decrease due to the growth. At the start of fall (October 1st), TEQ concentrations in grass start to increase again. Note that this example is solely for illustration purposes. Congener-specific grass concentrations were used to model exposure.

$$c_{grass}(t) = \begin{cases} \left(\min\left(c_{grass,\min} \times e^{k_{grass}\times\left(t-t_{winter}+365\right)}, c_{grass,\max}\right)\right) & t < t_{summer} \\ \left(\max\left(c_{grass,\max} \times e^{-k_{grass}\times\left(t-t_{summer}\right)}, c_{grass,\min}\right)\right) & t \geq t_{summer}\ \&\ t < t_{winter} \\ \left(\min\left(c_{grass,\min} \times e^{k_{grass}\times\left(t-t_{winter}\right)}, c_{grass,\max}\right)\right) & t \geq t_{winter} \end{cases} \quad (12)$$

Here, t is the time (in days), which starts at 0 on January 1st of a given calendar year. $c_{grass,max}$ and $c_{grass,min}$ denote the maximum (i.e. in winter) and minimum (i.e. in summer) dioxin and dl-PCB concentrations in grass. The congener-specific grass concentrations used in this study (Table S4) were partially based on empirical data reported in Hoogenboom et al. (2022b) and partially based on measurements obtained in the present study (Additional File 1). k_{grass} is the experimentally determined exponential 'dilution through growth' factor of dioxins and dl-PCBs in growing grass. This factor was assumed to be 0.023 d^{-1}, based on a half-time of 30 days reported by Traag et al. (2006) for two locations close to an industrial area. Due to a lack of data, we assumed that this dilution factor was also representative of the Dutch floodplains. t_{summer} is the start of the spring and summer season (April 1st), t_{winter} is the start of the fall and winter season (October 1st), and t indicates the number of days that have passed in the calendar year of interest.

Essentially, these equations describe the process in which dioxin and dl-PCB concentrations in grass increase from the 1st of October until the 1st of April until a concentration of $c_{grass,max}$ is reached. Then, from the 1st of April until the 1st of October, the concentration decreases again through dilution, until a concentration of $c_{grass,min}$ is reached. An important assumption here is that the dilution rate of dioxins and dl-PCBs in grass through growth is equal to the rate in which the dioxin and dl-PCB concentrations increase again after summer. A visualization of the variations in grass concentration is given in Figure 2.

In contrast to the dioxin and dl-PCB concentrations in grass, the concentrations in soil, c_{soil}, are assumed to be constant over time. Furthermore, since no information was available on the dioxin and dl-PCB concentrations in milk, it was assumed in the present study that there was no exposure to dioxins and dl-PCBs *via* milk in the first 6 months of life. The practical consequences of leaving out the exposure *via* milk is addressed in the discussion section.

TEFs and TEQs

As explained in the introduction section, the dioxin and dl-PCB TEQ can be calculated using TEF values. Currently, maximum TEQ levels (Commission Regulation 2023) allowed in

Figure 3. Map of the Netherlands with an overview of the main rivers and the locations of the two studied floodplains.

muscle fat are based on TEF-values that were published in 2005 (Van den Berg et al. 2006). However, it must be noted that these TEF-values were revised in 2022 (DeVito et al. 2024), which will most likely lead to a revision of the maximum TEQ levels allowed in muscle fat. In principle, the presented model can be used to calculate TEQ levels in muscle fat based on both the 2005-TEF values and the revised 2022-TEF values. However, since the current maximum TEQ levels are still based on 2005-TEF values, the remainder of this documentation will be focused solely on the calculation of TEQ values using 2005-TEF values.

Model calibration

Relevant model parameters were calibrated such that a set of parameter values was obtained for each individual congener found in grass and soil samples in two Dutch floodplains along the Waal River, Beuningen, and Loevestein (Figure 3). In addition, as a comparison, parameters based on total-TEQ concentrations were also calibrated.

For the model calibration, we used a so-called nested sampling Monte Carlo algorithm (Buchner 2016, 2019), using the *Ultranest* package (Buchner 2021) and 400 live points. *Ultranest* is a Python package, which was employed within the programming language R (R Core Team 2021) using the R-package *reticulate* (Ushey et al. 2023).

Five relevant parameters were calibrated for each congener: (1) the absorption fraction of dioxin and dl-PCB congeners *via* grass and soil, f_{abs}, (2) the blood:fat partition coefficient, $p_{adipose}$, (3) the blood:liver partition coefficient, p_{liver}, (4) the blood:slowly perfused partition coefficient, p_{slow}, and (5) the metabolic rate constant, *kMet*,

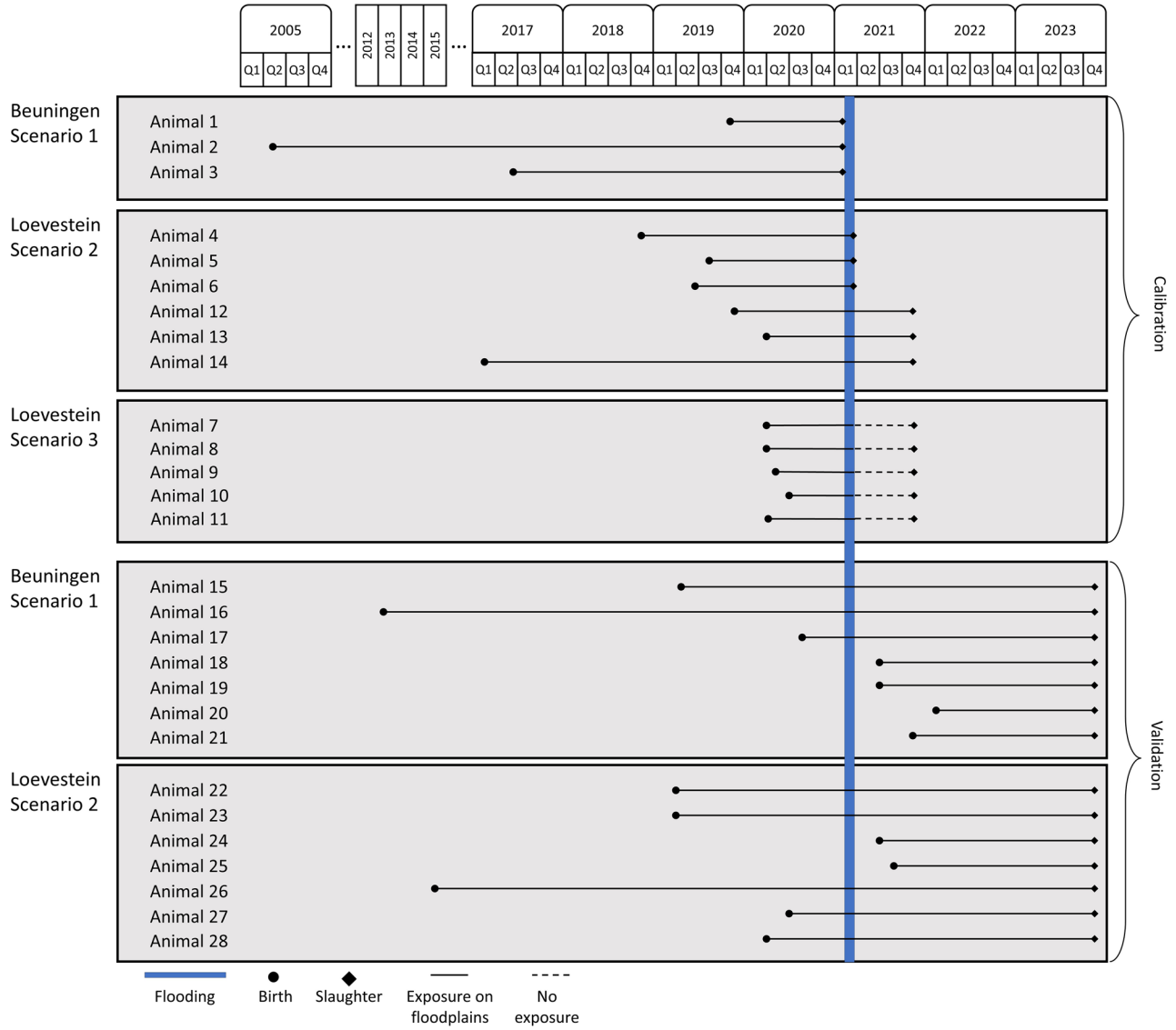

Figure 4. Exposure timeline of cattle that had been grazing in the Dutch floodplains. Tissue samples of these cattle were used for calibration and validation of the PBK model presented in this study.

that is used to calculate the hepatic clearance rate (Equation 7).

Furthermore, the relative size of the adipose tissue compartment was calibrated for bulls, as little information is available in the literature about the fraction of fat in free-ranging bulls (Supplemental Materials; Table S3). However, since the adipose fraction is a physiological parameter, rather than a congener-specific parameter, it was chosen to estimate this value only once. Specifically, the total-TEQ was used to determine the relative volume of the adipose compartment. This value was subsequently fixed for the individual congeners. Technical details on the model calibration and the resulting parameter values can be found in the Supplemental Materials (Section 4).

The calibration was performed using measured dioxin and dl-PCB levels in kidney fat, liver, and blood fat of Rode Geus cattle (Figure 4; animals IDs 1–14) that had been grazing at two different floodplains: Beuningen and Loevestein, both along the Waal River (Hoogenboom et al. 2022a, 2022b). However, five bulls from the Loevestein area were moved to a stable from April till November (see description of exposure scenario 3 below). Blood samples were taken from these bulls at three different time point before slaughter. Dioxin and dl-PCB levels that were below the limit of quantification (LOQ), were assumed to be equal to LOQ/2.

The available dioxin and dl-PCB levels used for model calibration are provided in Additional File 1.

To perform the calibration using the measured dioxin and dl-PCB levels, exposure scenarios needed to be defined. To this end, dioxin and dl-PCB concentrations in grass and adhering soil were taken from a previous publication of Hoogenboom et al. (2022b). In addition to these values, additional grass and soil measurements were conducted in this study (see Additional File 1).

Three different exposure scenarios were defined to reflect the exposure of the cattle that were investigated (Figure 4). Exposure scenario 1 was used for cows grazing at the floodplains of Beuningen (animal IDs 1–3). In this scenario, the grass concentrations in summer and winter, $c_{grass,min}$ and $c_{grass,max}$, respectively, were obtained by averaging the available summer and winter grass samples from Beuningen, respectively. The soil concentration (c_{soil}) was obtained by averaging all available soil samples from Beuningen. For this scenario, a continuous exposure to dioxin and dl-PCB congeners *via* grass and soil was modelled.

Exposure scenario 2 was used for the cattle that were continuously exposed to dioxins and dl-PCBs at the floodplains of Loevestein (animal IDs 4–6 and 12–14). In this scenario, due to a limited number of grass samples from Loevestein, the same minimum and maximum grass concentrations were used as for scenario 1 in Beuningen. The soil concentration used for this scenario was derived by averaging all available soil samples from Loevestein.

Exposure scenario 3 was used for the five 1-year-old bulls that were moved to a stable on 1 April 2021, after living on the floodplains of Loevestein for ~1 year (animal IDs 7–11). For the initial grazing period, the same dioxin and dl-PCB concentrations in grass and soil were used as for scenario 2. After being moved to a stable, the bulls were fed with clean feed and no adhering soil. The dioxin and dl-PCB concentrations in the feed, $c_{grass,clean}$, were assumed to be 0 ng/kg d.m. for each congener.

In February 2021, a flooding took place that resulted in a temporary coverage of the vegetation with sludge and increased exposure of the animals. To account for this, an elevated exposure *via* adhering soil was modelled for the cattle that were grazing in the floodplains at the time. Specifically, a soil consumption of 66% of the grass consumption was modelled between 1 February 2021 and 28 February 2021. Since the cows used for the calibration, that had been grazing in Beuningen, were slaughtered on 2 February 2021, this elevated soil consumption was only modelled for cattle grazing in Loevestein. The 66% soil consumption is based on the soil consumption after flooding of the floodplains estimated by Hoogenboom et al. (2022a). This increased consumption was estimated based on the difference between the TEQ levels in grass and soil levels before and after flooding of the floodplains. The grass and soil concentrations associated with each exposure scenario are specified in the Supplemental Materials (Table S4).

Model validation

Model validation was performed using dioxin and dl-PCB concentrations measured in kidney fat samples of cattle from Beuningen and Loevestein that were slaughtered in October and November of 2023 (Figure 4; Animal IDs 15–28). It must be noted that it was explicitly assumed that dioxin and dl-PCB concentrations in kidney fat are representative of the concentrations in muscle fat. For several animals we found that lipid-based dioxin and dl-PCB levels in adipose tissue and muscle fat were similar (data not shown). Therefore, it was assumed that dioxins and dl-PCB distribute homogenously over all fatty tissues.

The same exposure scenarios were assumed as for the cattle used for calibration, i.e. scenario 1 for Beuningen and scenario 2 for Loevestein (Supplemental Materials; Table S4). The modelled flooding incident in February 2021 was also modelled, except for animals not yet born at that time or still drinking from the mothers and not consuming grass.

Transfer of dioxin and dl-PCB congeners was modelled and compared to the observed concentrations in kidney fat samples of 14 animals (2023) by applying both the total-TEQ and the congener-specific approaches.

Due to the lack of data on plausible dioxin and dl-PCB concentrations in milk consumed by calves younger than 6 months, it was decided to omit simulated concentrations from the first year of the animal's life from the analyses. The choice of the 1 year-period was based on the analysis of the muscle fat concentrations, which showed that the effect of leaving out exposure *via* milk on the muscle fat concentration is negligible for cattle older than 1 year.

Sensitivity analysis

A local sensitivity analysis was performed to determine the most sensitive model parameters. To this end, we simulated dioxin and dl-PCB concentrations over time in muscle fat and subsequently determined the change in the area under the curve (AUC) resulting from a change in the model parameter values. Specifically, we computed a normalized sensitivity coefficient, S, to determine the sensitivity of the AUC to the model parameters:

$$S = \frac{\frac{\Delta AUC}{AUC}}{\frac{\Delta p}{p}} \tag{13}$$

with ΔAUC representing the change in the AUC as a result of a change in the parameter value, Δp. In this work, $\Delta p/p$ was set at 0.1, which essentially means that we increased a parameter value with 10%. Important to note is that the normalized sensitivity coefficients were computed separately for each parameter. Combinations and/or correlations between parameters were not taken into account.

Code and accessibility

The source code is publicly available at www.github.com/rivm-syso/dioxins-wild-cattle. In addition, the model has been made publicly accessible as a webtool on feedfoodtransfer.nl. This webtool contains a user-friendly interface to the PBK model, allowing potential users, such as risk assessors, risk managers, and researchers, to easily manage the models without the need of having a programming background.

Results

The PBK model described in the previous section was used to estimate muscle fat concentrations of individual dioxins and dl-PCBs, as well as TEQ of the cattle grazing in the floodplains in Beuningen and Loevestein. The estimated concentrations were validated using the measured concentrations in kidney fat described in Additional File 1. To illustrate the added value of the congener-specific modelling approach, the results of both the congener-specific approach and the total-TEQ approach are presented.

Calibration of parameters

Five relevant PBK model parameters were calibrated in this study. Figure 5 provides a visualization of the median values as well as the interval between the 5th and the 95th percentiles of the possible parameter values. Clear differences were observed between various congeners. For example, the metabolic rate constant, *kMet*, was substantially lower for the majority of dl-PCBs compared to the dioxins. Furthermore, the estimated absorption coefficient was close to 1 for most congeners, but below 0.5 for 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, OCDF, and PCB 77. This is consistent with the fact that 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, and OCDF levels measured in kidney fat, blood fat, and liver were mostly below the LOQs, whereas they were measured above the LOQs in grass and soil.

Model validation

Results of the model validation are shown in Figures 6 and 7. As demonstrated in Figures 6 and 7, the estimated sum-TEQ and total-TEQ concentrations in muscle fat align reasonably well with the corresponding measured concentrations in kidney fat of animals sampled in the fall of 2023. Table 1 shows a comparison between the estimated and measured TEQ levels in the samples of the cattle that had been grazing in the floodplains of Beuningen and Loevestein in the fall of 2023. Overall, the congener-specific PBK approach tends to overestimate the TEQ levels, on average by a factor of 2.4. For the total-TEQ approach, this difference is slightly higher, i.e. on

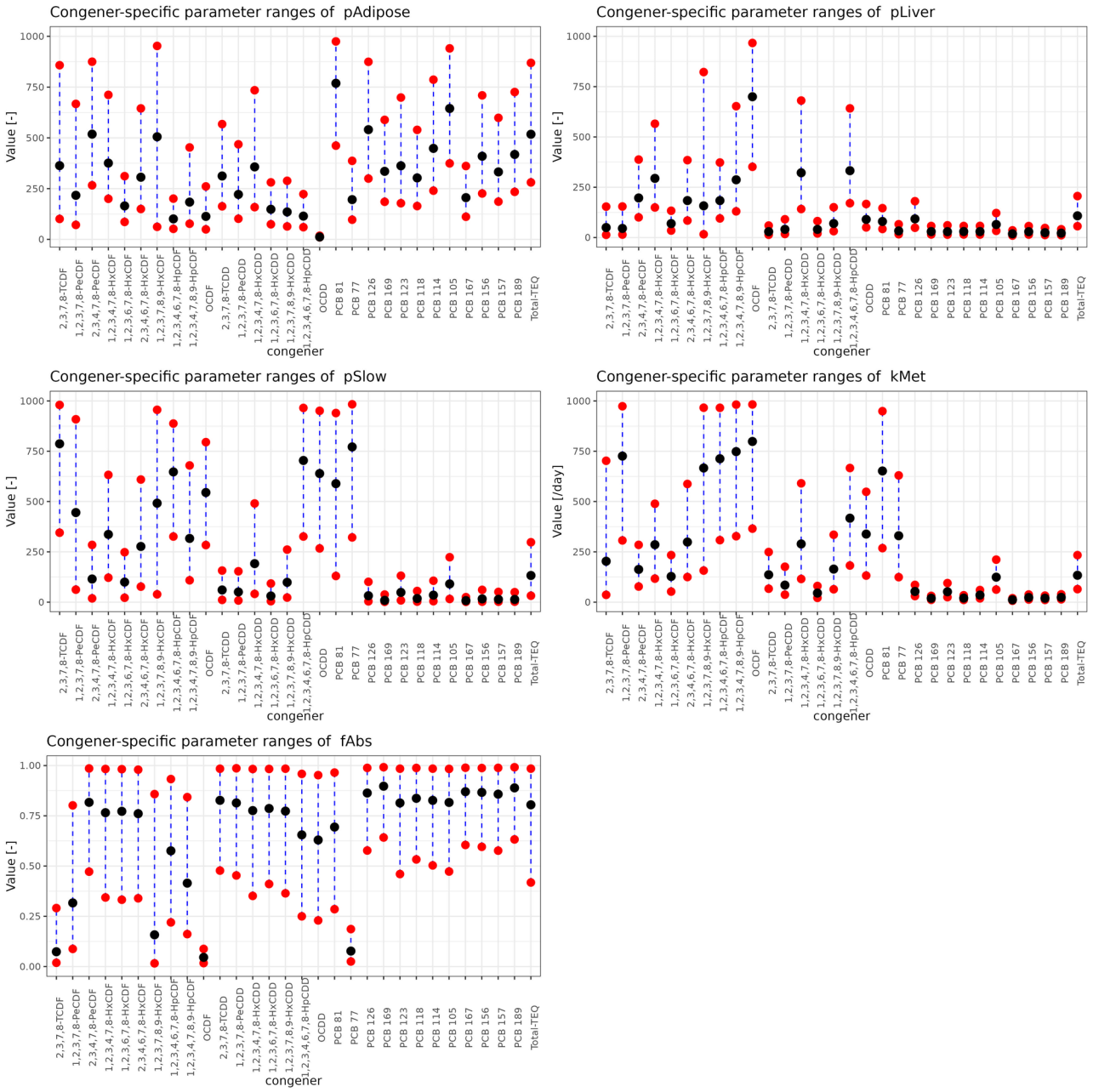

Figure 5. Median values (black dots) and 5th and the 95th percentiles (lower and upper red dots respectively) of the posterior likelihood distributions for each calibrated PBK model parameter and each congener.

average a factor of 2.7. Both the congener-specific and the total-TEQ approach result in accurate predictions of TEQ levels in muscle fat of the three bulls from Beuningen, with differences between estimated and measured TEQ levels that are within a factor of 1.5. This was also the case for the predictions with the congener-specific approach for three cows in Loevestein (Table 1; animal IDs 24, 26, 27). Interestingly, these three cows were estimated to have a body fat content of 30–40% and at least two of them did not calve in the year they were slaughtered. This is important since the model takes into account the elimination of dioxins and dl-PCBs due to milk production and as such is expected to underestimate the muscle fat levels in these cows. The total-TEQ levels in 4 out of the remaining 8 cows were overestimated by more than a factor 3. The congener-specific validation results are given in Table S5. The predicted effect of the flooding in 2021 can be seen in Figures 6 and 7. In February 2021, a high peak in estimated muscle fat

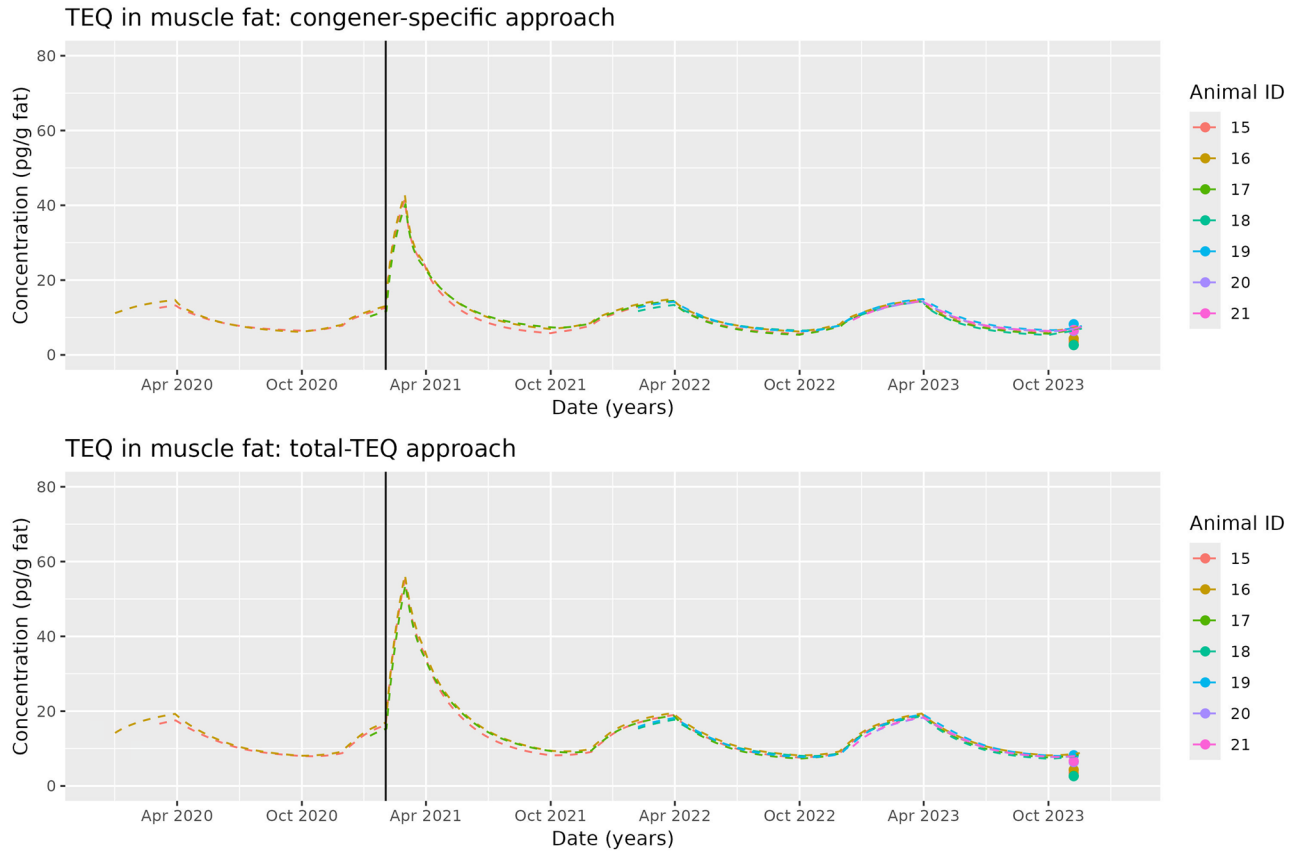

Figure 6. Estimated (dashed lines) and measured (dots) TEQ concentrations in muscle fat and kidney fat respectively of cattle that had been grazing in Beuningen, exposure scenario 1 (IDs 15–21). The vertical line represents the moment of the flooding. Note that measurements in kidney fat are used as a proxy for (estimated) concentrations in muscle fat. In the upper panel the estimated TEQ concentration in muscle fat is shown obtained by the congener-specific approach. In the bottom panel the estimated TEQ concentrations in muscle fat obtained by the total-TEQ approach are compared to the measured TEQ concentrations in kidney fat. All concentrations are expressed as pg TEQ/g fat. Note that the animals were born at several points in time, causing the lines to commence at various time points. Simulated concentrations in the first year of life are not shown due to uncertainties related to the dioxin and dl-PBC exposure *via* milk of calves.

concentration was predicted due to the increased soil consumption. In the short period after the flooding, the sum-TEQ concentrations in muscle fat increased by a factor of ~3–4. After this period of increased soil consumption, it took ~8 months until the muscle fat concentrations dropped to the regular levels.

Sensitivity analysis

The results of the sensitivity analysis are presented in Figure S2 (Supplemental Materials). For both cows and bulls the sensitivity analyses of the muscle fat concentrations show that relative liver volume (*rVLiver*), the metabolic rate constant (*kMet*), and the adipose: blood partition coefficient (*pAdipose*) are the most sensitive model parameters. Moreover, exposure parameters, such as the fraction of grass consumption with respect to the body weight (*iGrassFraction*) and the absorption fraction (f_{abs}) are also highly important. Interestingly, the relative liver volume (*rVLiver*) seems to be the most sensitive parameter of all compartment volumes. This is related to the fact that a higher liver volume leads to a larger amount of dioxins and dl-PCBs being cleared through metabolic processes. This in turn leads to lower dioxin and dl-PCB concentrations in the liver, thus explaining the large negative sensitivity coefficient for the relative liver volume.

Discussion

This study presents a PBK model to estimate the distribution and accumulation of dioxins and dl-PCBs in free-ranging cattle grazing in the

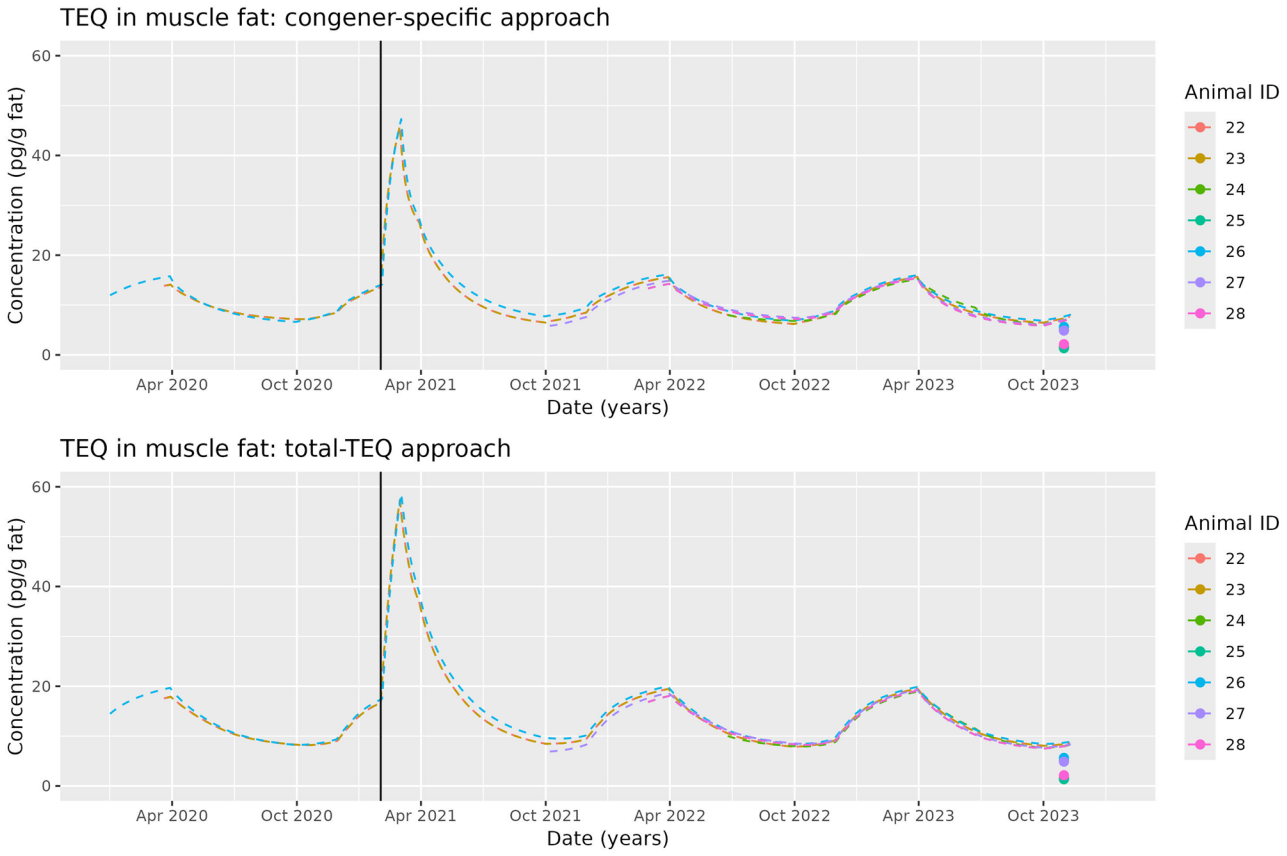

Figure 7. Estimated (dashed lines) and measured (dots) TEQ concentrations in muscle fat and kidney fat respectively of cattle that had been grazing in Loevestein, exposure scenario 2 (IDs 22–28). The vertical line represents the moment of the flooding. Note that measurements in kidney fat are used as a proxy for (estimated) concentrations in muscle fat. In upper panel, the estimated TEQ concentration in muscle fat is shown as obtained by the congener-specific approach. In bottom panel, the estimated TEQ concentrations in muscle fat obtained by the total-TEQ approach are compared to the measured TEQ concentrations in kidney fat. All concentrations are expressed as pg TEQ/g fat. Note that the animals were born at several points in time, causing the lines to commence at various time points. Simulated concentrations in the first year of life are not shown due to uncertainties related to the dioxin and dl-PBC exposure *via* milk of calves.

Table 1. Measured and predicted TEQ levels in muscle fat using both the congener-specific approach and the total-TEQ approach.

		TEQ level (pg TEQ/g muscle fat)			Ratio	
		Measured	Predicted		predicted/measured	
Location	Animal ID		Congener-specific approach	Total-TEQ approach	Congener-specific approach	Total-TEQ approach
Beuningen	15	3.5	6.9	8.3	2.0	2.3
	16	4.3	7.3	8.6	1.7	2.0
	17	2.8	6.8	8.1	2.5	3.0
	18	2.6	6.5	7.9	2.5	3.0
	19*	8.4	7.2	8.2	1.1	1.0
	20*	6.4	7.0	8.0	0.9	1.2
	21*	6.7	7.0	8.0	1.0	1.2
Loevestein	22	1.8	7.3	8.4	4.3	4.9
	23	1.6	7.3	8.4	4.6	5.3
	24**	5.1	7.0	8.4	1.4	1.6
	25	1.4	6.8	8.0	5.1	5.9
	26**	5.6	7.7	8.7	1.4	1.5
	27**	4.9	7.0	8.1	1.4	1.7
	28	2.2	6.8	8.0	3.2	3.7
Mean					2.4	2.7

In addition, the ratio between predicted and measured TEQ levels is provided.
*Bulls, rest of the animals are cows.
**Cows with high estimated body fat content (>30%).

Dutch floodplains. The current model incorporates physiological characteristics of Rode Geus cattle, a different breed than the differ typical dairy cattle in the Netherlands. Furthermore, congener-specific kinetic parameters were calibrated to provide more accurate estimates of the TEQ levels in muscle fat of the Rode Geus cattle. Model validation was performed for two floodplains along the same river and similar grass and soil levels (Figure 3). Generally, the developed PBK model produced reasonably accurate predictions of the dioxin and dl-PCB concentrations in muscle fat, with differences between predicted and measured concentrations that were, on average, a factor 2.4 higher for the congener-specific approach and 2.7 for the total-TEQ approach.

In the present study, five kinetic parameters of the PBK model were calibrated based on estimated exposure and measured dioxin and dl-PCB concentrations in various tissues (Figure 5). Interestingly, for 23 of the 29 congeners the estimated absorption fractions were substantially higher than the absorption fraction that was previously assumed for total-TEQ (i.e. 0.15 for grass and 0.50 for soil) in high productive dairy cows (Traag et al. 2006). In addition, the estimated metabolic rate constants of dioxins were substantially higher than the metabolic rate constant derived for dairy cows Derks et al. (1994) for 2,3,7,8-TCDD (i.e. 14 d^{-1}). The most likely reason for this finding is that the calibration in this study included data of dioxin and dl-PCB levels in blood fat at three different time points of cattle after they were moved to a stable with clean feed. These data provided valuable information on the clearance of dioxins, which was not available in the study of Derks et al. As such, this data helped to improve the estimate of the metabolic rate constant of dioxins.

In contrast to dioxins, the estimated metabolic rate constants of dl-PCBs were generally lower and more similar to the metabolic rate constant that was previously derived by Derks et al. for 2,3,7,8-TCDD (Derks et al. 1994). The lower metabolic rate constants could explain the observed higher contribution of dl-PCBs to the TEQ levels in muscle fat compared to soil and grass (Hoogenboom et al. 2022a). However, this slower elimination was less clear from the bulls from Loevestein that were kept in a stable. Specifically, during the first 2.5 months in the stable. Hoogenboom et al. (2022a) observed a decrease of 93% for the dioxin-TEQ and 91% for the dl-PCB-TEQ levels in blood, thus indicating little to no difference in metabolic clearance between dioxins and dl-PCBs. Despite the differences in metabolic clearance rates estimated in this study, differences in absorption of the individual congeners may better explain this observation.

For some congeners, levels measured in kidney fat, blood fat, and liver were below the LOQ. This applies specifically for the congeners 2,3,7,8-TCDF, 1,2,3,7,8 PeCDF, and 1,2,3,7,8,9-HxCDF. In addition, the congeners 1,2,3,4,7,8,9-HpCDF, OCDF, and PCB 123 were below the LOQ in most samples. For most of these congeners, the estimated absorption fractions were relatively low compared to other congeners, whereas the estimated metabolic clearance constant was relatively high (Figure 5). These parameter values should, however, be interpreted with caution, due to the correlation between the two parameters. The low tissue concentrations can be explained by either very low absorption fractions or very high metabolic clearance rates. However, since the exact tissue concentrations are unknown for these congeners, it is impossible to accurately determine the exact values for these parameters. The low tissue concentrations indicate that these congeners are less persistent in these animals and as such contribute less to the TEQ levels in muscle fat.

All absorption fractions calibrated in this study are higher than those previously estimated by Moenning, Lamp, et al. (2023) for dairy cattle. However, the model presented by Moenning, Lamp, et al. (2023) did not incorporate metabolism as a possible clearance route. Instead, they assumed that any metabolic elimination was implicitly accounted for by the absorption coefficients. This assumption most likely results in a decrease in the estimated absorption fraction, thus explaining the differences with the absorption fractions estimated in the present study.

Based on the estimated congener-specific PBK parameters, model validation was performed based on measured dioxin and dl-PCB concentrations in kidney fat of cattle grazing in floodplains at Beuningen and Loevestein. In all cases, the

model was able to describe the data reasonably well, and the model predictions were generally close to the measured concentrations (Table 1). For some congeners, the measurements showed large inter-animal variations that were not fully captured by the model (Supplemental Materials, e.g. Figures S16, S24, S27, S28, S32). A plethora of factors may relate to these variations, including differences in exact grazing locations, differences in body compositions (fat fraction) and weights, differences in milk production in case of cows, and differences in feed consumption. Since the PBK model predicts dioxin and dl-PCB concentrations for a typical bovine breed grazing in the floodplains, such inter-animal variations are not included. Nevertheless, the predicted total-TEQ levels in muscle fat using the congener-specific approach were on average a factor of 2.4 higher, and always within a factor of 5.1 of the measured levels (Table 1).

The results shown in Table 1 also show that the congener-specific approach, which takes into account differences between kinetics of individual congeners, should be preferred over the total-TEQ approach. The relative differences between estimated and measured TEQ levels in muscle fat are lower for the congener-specific approach (factor 2.4) than for the total-TEQ approach (factor 2.7). A factor 2 difference between estimated and measured concentration is generally considered 'good' for PBK models (Puttrevu et al. 2020; Zazo et al. 2022). It must be noted that the PBK model presented in this study generally overestimated TEQ levels in muscle fat with both the congener-specific approach and the total-TEQ approach.

In the present study, exposure to dioxins and dl-PCBs *via* milk was left out of the analyses, due to a lack of a priori information on dioxin and dl-PCB levels in milk of cattle grazing in the Dutch floodplains. A practical implication of this omission is that the model presented in this study underestimates the total-TEQ concentration in muscle fat for the first 6 months of calves' lives, when milk consumption is expected. Furthermore, in the months following the expected milk consumption an underestimation of the TEQ concentration in muscle fat is also expected. From visual inspection of Figures 6 and 7, it can be seen that the muscle fat concentrations are very similar between the different animals after the age of 1 year. Therefore, leaving out exposure *via* milk during the first 6 months after birth is considered to have a negligible effect on the muscle fat concentration of calves at the age of one year and onwards. Furthermore, since model validation is this study was performed for cattle older than 1 year, the omission of exposure through milk likely had little to no effect on the (quantitative) performance evaluation.

A limitation of this study is that the available data were not sufficient to calibrate every sensitive model parameter. For example, the clearance rate to milk, cl_m, and the blood: richly perfused organ partition coefficient, $p_{richly\ perfused}$, could not be estimated with these data because there were no dioxin and dl-PCB measurements available in milk or in richly perfused tissues. In addition, in the calibration we assumed that the absorption from grass is equal to the absorption from soil. Since there are no data available where free-ranging cattle were solely exposed to grass or soil, it is impossible to fit two separate absorption fractions for these matrices.

Besides the absorption of dioxins and dl-PCBs, another fairly uncertain parameter in the model is the soil consumption. During regular grazing (i.e. no floodings), it was assumed that the consumption of soil is 4% of the dry matter grass consumption during the summer period, and 8% during the winter period. A soil consumption of 4% of the grass consumption was previously used by Traag et al. (2006). It is reasonable that the consumption of adhering soil is higher in the winter period than in the summer period since grass is generally shorter in winter. These soil consumption percentages are in line with the percentages reported by Jurjanz et al. (2012), who observed that the soil consumption of dairy cattle with access to pastures was, on average, between 2.7 and 3.7% of the total feed consumption, whereas the highest soil consumption was 10.4% of the total feed consumption.

Finally, further validation of the model should ideally be performed using data from additional tissues and timepoints. In this study, validation was performed using kidney fat samples from

two different floodplains, all obtained in the fall of 2023. To further validate the model, additional liver fat, milk fat, and/or blood fat samples would help to verify whether the model also accurately predicts dioxin and dl-PCB concentrations in those tissues. Furthermore, to ensure that the seasonal variations in dioxin and dl-PCB concentrations are correctly modelled, tissue or blood samples from various time points are needed.

An important aspect of the presented PBK model is that age and growth are taken into account, as well as the exact date of birth. These features are particularly important when the exposure scenario also heavily depends on temporal changes, as is the case for the Dutch floodplains (e.g. peak exposure after flooding, more soil consumption in winter). The model presented in this study was designed and validated to estimate individual dioxin and dl-PCB concentrations in muscle fat of cattle grazing in the Dutch floodplains. These concentrations can be expressed as toxic equivalents of 2,3,7,8-TCDD, based on TEF2005 (Van den Berg et al. 2006) and TEF2022 values (DeVito et al. 2024). Since our approach considers individual congeners, there is no need to recalibrate the model parameters when MLs are revised based on the TEF2022 values. Instead, the posteriori calculation of the TEQ concentration can simply be adjusted according to the revised TEF values.

This paper presents a PBK model to estimate the distribution and accumulation of dioxins and dl-PCBs in cattle grazing in floodplains. The model validation generally demonstrated that the model is adequate and can estimate tissue concentrations in cattle. The model will be made publicly available as a webtool with a user-friendly interface on www.feedfoodtransfer.nl. By providing representative dioxin and dl-PCB concentrations in grass and soil of a particular grazing area, users will be able to estimate total-TEQ concentrations in muscle fat over time. As such, this PBK model may help to better understand the relation between environmental dioxin and dl-PCB levels and those in the animals and may provide relevant insights for risk assessment and risk management.

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Disclosure statement

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