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A probabilistic model for the carry-over of PCDD/Fs from feed to growing pigs

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HIGHLIGHTS

- A pharmacokinetic model was combined with a probabilistic model to gain a decision tool for risk management.
- The German dioxin incident of winter 2010/2011 can be described by the tool.
- Clearing rates for the congener 1,2,3,4,7,8-HxCDD were determined from experimental data (Hoogenboom et al., 2004).
- The approach demonstrated here is a showcase how a risk assessment in the case of contaminated feeding can be performed.

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ABSTRACT

When food producing animals are contaminated with PCDD/F congeners, information on the contaminant's concentration in the bodies of the animals at time of slaughter is needed for risk management purposes. We have developed a mathematical model for the kinetics of PCDD/Fs in growing pigs in case of contaminated feed fed for a limited duration of time. This model allows the prediction of concentrations in body fat. It considers absorption fractions of PCDD/Fs, clearance by metabolism, dilution by growth and excretion through fecal fat. The model parameters were calibrated by fitting the model to experimental data. On the basis of this toxicokinetic model a probabilistic model has been constructed. The probabilistic model handles the parameters with appropriate probability distributions and Monte-Carlo simulation technique, providing for realistic situations with many animals and a range of contaminations and feeding intervals. We applied the new model to describe the German dioxin incident of winter 2010/2011 and discuss its viability as decision tool. The approach demonstrated here is a showcase how a risk assessment in the case of contaminated feeding can be performed.

1. Introduction

Contaminations of animal feed for food producing animals with PCDD, PCDF and dioxin-like PCB have recurred irregularly, for instance 1999 in Belgium (Van Larebeke et al., 2002), 2008 in Ireland (Heres et al., 2010) and 2010/2011 in Germany (Abraham et al., 2011). As a result of the toxicological properties of PCDD, PCDF and dioxin-like PCB this is of public health concern (WHO, 2010). During the German dioxin incident of 2010/2011, a quantitative assessment was needed to study the kinetics of PCDD/Fs in pigs. Previous models looked at worst-case or specific scenarios (Fries, 1996; Hoogenboom et al., 2007). To investigate all possible outcomes and scenarios, a more general model was needed. We constructed a probabilistic model by combining a toxicokinetic model with a Monte-Carlo simulation, where all important parameters were modeled using probability distributions. This probabilistic model is capable of providing risk assessment in the case of future dioxin incidents. Beyond that, it can help to prevent gratuitous culling and to avert further damage to farmers.

The model is calibrated with the experimental data of Hoogenboom et al. (2004), who conducted a feeding experiment with growing pigs using diluted feed from the dioxin crisis in Belgium in 1999. Furthermore, we refer to the following studies: Lenk (2007), who accomplished a similar feeding experiment as Hoogenboom et al. (2004) with three different concentrations of a PCDD/F mixture; Shen et al. (2012), who repeated Lenk's experiment and constructed a prediction formula for the PCDD/F content in food; and Spitaler et al. (2005), who fed pigs with contaminated feed of different concentrations of a PCDD/F mixture and measured the PCDD/F concentrations in different tissues. Previous theoretical approaches with point estimates were made by Fries (1996), who used a kinetic one-compartment model without considering metabolic clearance, excretion and uncertainty, and Hoogenboom et al. (2007), who performed simulations of PCDD/F concentrations in growing pigs with a two-compartment

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model. Although these kinetic models differ from our model, they were used as an additional test for the validity of ours.

2. Materials and methods

In the German dioxin incident of winter 2010/2011 a peculiar mixture of PCDD/F congeners was observed in contaminated feed. The toxic equivalent (TEQ) level (Van den Berg et al., 1998) was mainly caused by two hexachlorodibenzo-p-dioxins (1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD). Both congeners also were present in the experiment of Hoogenboom et al. (2004), but their concentrations in body fat are too close to the limit of detection, or even below. In the experiment of Hoogenboom et al. (2004) the congener 1,2,3,4,7,8-HxCDD was present in a higher concentration, hence we use these data to calibrate our kinetic model of the pig. Under the assumption that the three HxCDDs behave similarly due to their similar chemical structure, the model can be used to simulate the German incident. Hoogenboom et al. (2004) used diluted feed from the Belgian dioxin crisis in 1999. During the experiment, growing pigs were fed for one week with contaminated fodder. Afterwards, they were kept under normal conditions up to an age of 6 months. At six time points after exposure, samples of back fat were taken by biopsy and analyzed. Lenk (2007) conducted a similar feeding experiment with three groups of pigs and three different concentrations of a PCDD/F mixture. We performed the same model-fit with their data as we did with the data of Hoogenboom et al. (2004).

2.1. Model description

The present model describes the kinetics of PCDD/F carry-over from feed to body fat of growing pigs. Generally, measured PCDD/F values are related to fat, concerning the highly lipophilic character of PCDD/Fs. Samples from different tissues of the same individual usually agree very well due to homogeneous distribution corresponding to fat content (Beck et al., 1994). Therefore, we use a pig model that consists of a single fat compartment of age dependent size. PCDD/F uptake and distribution in body fat is fast compared to characteristic times of PCDD/F elimination.

The total PCDD/F amount in the pig changes with PCDD/F intake with feed, metabolic clearance and excretion via faeces. The PCDD/F absorption fraction and metabolic clearance rate are estimated with this model from Hoogenboom et al. (2004) data. Since Hoogenboom et al. (2004) did not measure the body fat of the pigs, we use the values given in Pfeiffer et al. (1984). For the feed amounts we use values given in Staudacher (2010). The excreted amount of fat per day is assumed to be around 1 g (Guerciolini et al., 2001).

The change of PCDD/F amounts in body fat is described as sum of incoming and outgoing amounts of PCDD/F (Eq. (1)). The uptake by feed is described as the product of the PCDD/F concentration in feed, the daily feed portion and a constant absorption fraction. The amount of metabolized PCDD/Fs is calculated as a product of the total amount of PCDD/F in the pig and the metabolic clearance rate. The excreted amount is calculated by the product of PCDD/F concentration in body fat and fat excretion rate.

$$\frac{d}{dt}A(t) = C_I(t)\ I(t)\ k_{abs} - A(t)\ k_{cle} - C(t)\ k_{exc} \tag{1}$$

The symbols, their meaning and units are listed in Table 1. The amount of PCDD/F in a pig at the beginning of the fattening period is assumed to be zero. In the final analysis, we want to describe the PCDD/F concentration $C(t)$ in body fat of pigs. Therefore, we need to introduce functions for the feed quantity $I(t)$ and body fat $F(t)$ into Eq. (1) (Appendix A).

Table 1
Symbols, meanings and units.

Symbol	Meaning	Unit
$W(t)$	Body weight	kg
$F(t)$	Body fat	kg
$I(t)$	Daily feed intake	kg d^{-1}
$A(t)$	Total amount of PCDD/F in a pig	ng
$C(t)$	PCDD/F concentration in body fat	pg g^{-1}
$A_I(t)$	PCDD/F amount in feed	ng
$C_I(t)$	PCDD/F concentration of feed dry matter	ng kg^{-1}
k_{abs}	Absorption fraction	–
k_{cle}	Metabolic clearance rate	d^{-1}
k_{exc}	Excretion rate via feces	g d^{-1}

2.2. Growth functions and feed function

The body weight is described by a power function with offset (Eq. (2)) fitted to the data of Pfeiffer et al. (1984). As can be seen in Fig. 1 (left), body weight and body fat are highly correlated. We divided the experimental body fat by the experimental body weight and obtained the data of Fig. 1 (center), showing that the body fat fraction of pigs older than 75 d grows linearly with time. Using $F(t)/W(t) = f_1\ t$ for the fat fraction, we obtain Eq. (3) for the body fat. The amount of feed as function of body weight (Staudacher, 2010) converges to a constant and can be described by an exponential saturation function (Eq. (4)).

$$W(t) = w_0 + w_1\ t^{w_2} \tag{2}$$

$$F(t) = f_1\ t\ W(t) \tag{3}$$

$$I(W(t)) = i_1\ (1 - e^{-i_2\ W(t)}) \tag{4}$$

The coefficients of Eqs. (2)–(4) are listed in Table 2. The data fitting was performed with the Levenberg–Marquardt nonlinear regression algorithm (Marquardt, 1963), using the GNU Octave-function `leasqr` (Eaton et al., 2009, http://octave.sourceforge.net).

Substituting Eqs. (2)–(4) into the differential equation for the PCDD/F concentration in body fat yields a differential equation (Eq. (A.5)), that contains 9 parameters (w_0, w_1, w_2, f_1, i_1, i_2, k_{exc}, k_{abs}, k_{cle}). Five of these parameters are estimated from the fit of growth and feed functions (Table 2), the birth weight was set to $w_0 = 1.3$ kg (Pfeiffer et al., 1984) and k_{exc} is assumed to be 1 g d^{-1} (Guerciolini et al., 2001). Therefore two unknown parameters remain, k_{abs} and k_{cle}.

The differential equation for the PCDD/F concentration $C(t)$, Eq. (A.5), is solved with a finite-difference method, using constant time steps of 1 d. We compared this method with the more sophisticated Dormand–Prince method (Dormand and Prince, 1980), implemented in the GNU Octave-function `ode45` (Eaton et al., 2009, http://octave.sourceforge.net), and found only minor differences between the methods. Due to the better computing performance of the finite-difference method, we went further with that method.

2.3. Calibration of the model

To calibrate the model, the metabolic clearance rate k_{cle} and the absorption fraction k_{abs} of the differential equation Eq. (1) were fitted simultaneously to the experimental data of Hoogenboom et al. (2004) (Fig. 2, left). The fit was performed with the Levenberg–Marquardt algorithm (Marquardt, 1963), using the GNU Octave-function `leasqr` (Eaton et al., 2009, http://octave.sourceforge.net). For the absorption fraction we obtained the fit result $k_{abs} = 0.456$ +- 0.013 and for the metabolic clearance rate $k_{cle} = (3.8 \pm 1.6) \times 10^{-3}$ d^{-1} (Table 2), corresponding to a half life of $t_h = 180$ d with a 95%-error-interval of [100, 1040] d.