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Transfer model for cadmium in pig, version 2.0 - Model documentation

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Summary

The fundamentals of a feed-food transfer model for cadmium concentrations in kidney and liver of growing pigs are presented. The model, which is available as a webtool application (https://feedfoodtransfer.nl/), can be used to compare simulated concentrations with regulatory limits for these food matrices.

1 Introduction

Cadmium (Cd) is a heavy metal that poses significant human health risks, particularly through the consumption of animal-derived products contaminated via feed. The toxicological concern for cadmium is heightened by its tendency to accumulate in critical organs such as the liver and kidneys. Sources of cadmium contamination in animal feed are varied and include contaminated minerals (Sapunar-Postruznik et al. 2001), plants grown on polluted soils (Franz et al. 2008), and the use of contaminated sewage (Bache et al. 2007; Lisk et al. 1982) or manure (Lindén, Olsson, and Oskarsson 1999). Furthermore, direct intake of contaminated soil by animals can also contribute to elevated cadmium levels in animal tissues.

To safeguard consumer health, the European Union has established maximum cadmium limits for both feed and food products. Ensuring that feed concentrations remain below these thresholds is essential for maintaining compliance in products such as pig liver, and kidney.

Understanding the transfer of cadmium from feed to edible animal tissues is crucial for risk assessment, regulatory compliance, and incident management. Previous research on contaminants like dioxins, PCBs, and aflatoxin B1 (Hoogenboom et al. 2007; Hoogenboom et al. 2010; van Eijkeren, Bakker, and Zeilmaker 2006; Van Eijkeren et al. 2006) has demonstrated the value of mechanistic transfer models in linking feed concentrations to tissue residues. However, for cadmium, existing studies in growing pigs have not fully addressed the kinetics of exposure at multiple time points, nor the effect of switching from contaminated to clean feed.

The present documentation describes the development of a mechanistic model for cadmium transfer in growing pigs, focusing on the accumulation in the liver and kidney. This model is based on experimental data (Hoogenboom et al. 2015) and tracks cadmium levels in various organs and blood over time, including the role of metallothioneins (MTs), which are proteins integral to cadmium accumulation in tissues.

The cadmium transfer model presented here aims to improve our understanding of the feed-to-food transfer dynamics, support the evaluation of contamination incidents, and inform regulatory decisions to protect consumer health.

2 Model Description

2.1 General overview

A simple, one-compartment mechanistic transfer model was developed to describe cadmium concentrations in liver and kidney of growing pigs. This compartment essentially captures the amount of cadmium in the body over time. From that body burden, cadmium concentrations in liver and kidney can be derived.

2.2 Model equations

The transfer model described in this report consists of a differential equation that describes the rate of change in the amount of cadmium in liver or kidney over time.

$$\frac{dA_i(t)}{dt} = MT_i(t) \times \frac{\alpha_i \times D(t)}{\beta_i + D(t)} \quad (1)$$

Here, $A_i(t)$ (mg) is the amount of cadmium in tissue *i* (i.e., liver or kidney), $MT_i(t)$ is organ-specific metallothionein concentration (µmol/kg organ), α_i (kg organ/µmol) is a fitted parameter that is used to scale the MT levels in organ *i* to the cadmium uptake rate, β_i (mg/d) is a fitted parameter that can be considered as the overall saturable binding in the transport of cadmium from feed to organ *i*. Finally, $D(t)$ is the total cadmium dose taken in (mg/d). This cadmium dose is the sum of the background dose and a dose via contaminated feed. The α_i and β_i parameters were fitted based on data in Hoogenboom et al. (2015).

The organ-specific metallothionein concentration, $MT_i(t)$, varies over time and was found to be related to the organ-specific cadmium concentrations, $C_i(t)$, (mg/kg organ) (Verma et al. (1978)). The change of MT in organ *i* was calculated as follows:

$$MT_i(t) = MT_{0,i} + k_i \times C_i(t) \quad (2)$$

Here, $MT_{0,i}$ (µmol/kg organ) is the starting metallothionein level in organ *i*, before exposure and k (µmol/mg) denotes the increase in metallothionein level which depends on the cadmium concentration in organ *i*. The concentration $C_i(t)$ (mg/kg organ) is calculated as $C_i(t)=A_i(t)/V_i(t)$, with $V_i(t)$ representing the organ weight (kg) of organ *i* over time.

Since this model considers growing pigs, the organ weights, $V_i(t)$ increase over time. Similar to the metallothionein levels, a linear function was adopted to describe the growth in organ volumes:

$$V_i(t) = V_{0,i} + dV_i \times t \quad (3)$$

Here, $V_{0,i}$ (kg) is the starting weight of organ *i* and dV_i is the weight increase of organ *i* over time.

All the model parameters described above were fitted based on data acquired in a study conducted by (Hoogenboom et al. 2015)
The amount of feed consumed by the growing pigs was defined as a function of time. Various feed options are implemented based on the WFSR feed database[1]. The first option is total compound feed (blend of various raw materials and/or additives). In addition, one can also select one particular ingredient of the total compound feed. It was assumed that pigs start eating this type of total compound feed from an age of 28 days. The intake curve over time (d) is as follows.

$$A_{feed,total\_compound}(t) = \frac{0.88\times(0.0246\times t^2+9.9013\times t+330.44)\times f_{ingredient}}{1000} \quad (4)$$

With t representing the age in days and $f_{ingredient}$ being the fraction of the particular ingredient considered (user input; if applicable).

Another option is the intake of wet mixes (mixture of compound feed, solid and liquid by-products and water). It was assumed that pigs start eating this type of feed from an age of 66 days. This intake curve is:

$$A_{feed,wet\_mixes}(t) = \frac{0.25\times(-0.0496\times t^2+32.379\times t-911.2)}{1000} \quad (5)$$

To calculate the actual total Toxic Equivalents (TEQ) dose $D(t)$ that are consumed by the pigs on a daily basis, one can simply multiply the amount of feed (ingredient) with the total TEQ concentration in the feed (ingredient), C_{feed}.

$$D(t) = A_{feed}(t) \times C_{feed} \quad (6)$$

2.3 Model assumptions

The following assumptions were made in the presented model:

- Liver and kidney weight growth is linear over time for the duration of the animal experiment in Hoogenboom et al. (2015). In this experiment, 3-month old pigs were followed over a period of 12 weeks.
- The relationship between organ MT and organ Cd concentration is linear.
- Cadmium distributes homogeneously over liver tissue and over kidney tissue.

[1] https://wfsr.shinyapps.io/feeddatabase/

2.4 Parameter values

PBK model parameters that are used in the transfer model are shown in Table 1. For each model parameter, a reference is provided from which the value was obtained.

Table 1: Description of parameters fitted based on the data reported in Hoogenboom et al. (2015).

Table 1: Description of parameters fitted based on the data reported in Hoogenboom et al. (2015).

Parameter	Value [unit]	Description
α_{kidney}	0.051 [kg organ/µmol]	Scaling of MT levels in kidney to the cadmium uptake rate
α_{liver}	0.059 [kg organ/µmol]	Scaling of MT levels in liver to the cadmium uptake rate
β_{kidney}	12.4 [mg/d]	Saturable binding in the transport of cadmium from feed to kidney
β_{liver}	37.4 [mg/d]	Saturable binding in the transport of cadmium from feed to liver
$MT_{0,kidney}$	8.65 [µmol/kg organ]	Starting MT level in kidney before exposure
$MT_{0,liver}$	22.3 [µmol/kg organ]	Starting MT level in liver before exposure
k_{kidney}	0.923 [µmol/mg]	Increase of MT concentration with respect to kidney cadmium concentration
k_{liver}	0 [µmol/mg]	Increase of MT concentration with respect to liver cadmium concentration
$V_{0,kidney}$	0.114 [kg]	Starting kidney weight at birth
$V_{0,liver}$	0.626 [kg]	Starting liver weight at birth
dV_{kidney}	0.0256 [kg/d]	Kidney weight increase over time
dV_{liver}	0.100 [kg/d]	Liver weight increase over time

MT: metallothionein

3 Implementation details

The transfer model simulations were developed and run using the R modelling language and using the deSolve package. The model code is publicly available online (https://github.com/rivm-syso/cadmium-pig). Specifications on the software used are listed below:

Name software: R (v. 4.5.1)
Manufacturer: The R Foundation for Statistical Computing
Place of manufacture: online
Year of manufacture: 2025
Description: A programming language for statistical computing

Name software: DeSolve (tested with version 1.40)
Manufacturer: Karline Soetaert, Thomas Petzoldt and R. Woodrow Setzer
Place of manufacture: online
Year of manufacture: 2023
Description: Package to solve systems of differential equations
url: https://cran.r-project.org/web/packages/deSolve/index.html

4 Model applicability

The transfer model presented in this report can be used to simulate the carry-over of cadmium from feed to liver and kidney of growing pigs. As such, the model enables comparison of the estimated concentration to regulatory limits of this food matrix. Similarly, the model can be used to estimate the wash-out period needed to comply with regulatory limits in case the concentrations exceeded such regulatory limits.

An example of a model application is given in Figure 1. Exposure to 5 mg cadmium/ kg total compound feed was simulated. Exposure was simulated to start at an age of 56 days and a duration of 30 days. After the 30 days of exposure to contaminated feed, an additional 130 days were simulated in which feed with a background level of 0.1 mg cadmium/ kg feed was provided. The regulatory limits for cadmium are set at 0.5 mg/kg liver and 1.0 mg/kg kidney at the EU level according to the amended Regulation (EC) Nr. 1881/2006, subsection 3.2.

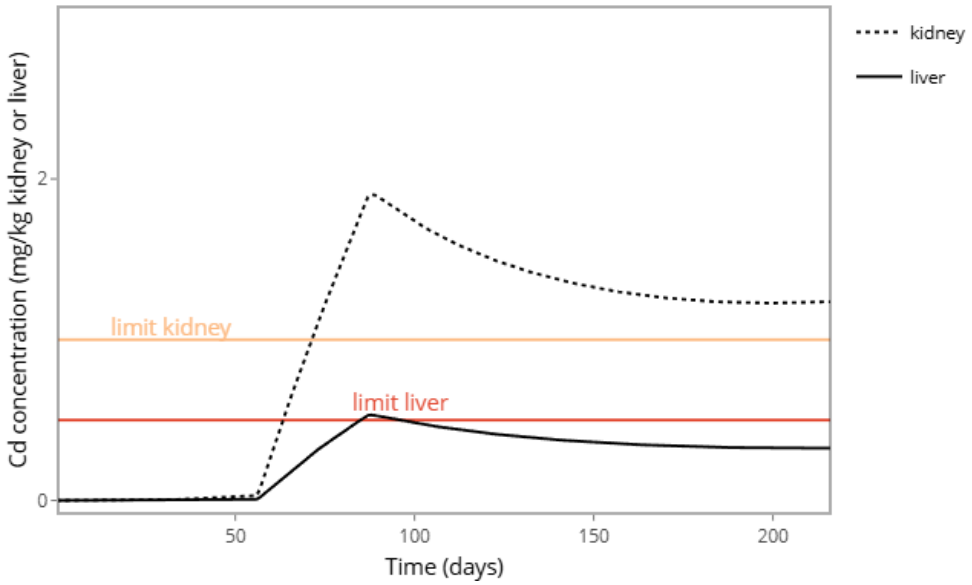

Figure 1 Simulated cadmium concentration in liver and kidney of growing pigs fed contaminated feed (5 mg cadmium/kg feed) during 30 days followed by feed with a background cadmium concentration of 0.1 mg/kg feed for 130 days.

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