



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

**Congener specific transfer model for
non-dioxin-like polychlorinated
biphenyls (ndl-PCBs) in laying hens,
version 1.1 - model documentation.**

2024
Sylvia Notenboom, Jordi Minnema

Colophon

© RIVM 2024

Parts of this publication may be reproduced, provided acknowledgement is given to the National Institute for Public Health and the Environment, and the title and year of publication are cited.

Sylvia Notenboom (author), RIVM
Jordi Minnema (author), RIVM

Contact:

feedfoodtransfer@rivm.nl

Contents

Summary—4

1	Introduction—5
2	Model description—6
2.1	General overview—6
2.2	Model equations—6
2.3	Model assumptions—8
2.4	Generic parameters—8
2.5	System-dependent parameters—8
3	Software details—11
4	Model applicability—12
5	References—13
Annex I: R-Code—14	

Summary

The fundamentals of a congener specific feed-food transfer model for non-dioxin-like polychlorinated biphenyl (ndl-PCB) concentrations in body fat and egg yolk fat in laying hens 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

Non-dioxin-like polychlorinated biphenyls (ndl-PCB) are persistent environmental pollutants (POPs) that may accumulate in fatty tissues of animals and humans. One of the main sources of human exposure to ndl-PCBs is the consumption of animal products, such as meat, milk and eggs. In turn, animal feed is an important contributor to the accumulation of ndl-PCBs in animal products used for human consumption.

This report presents the congener-specific transfer model that estimates ndl-PCB concentrations in body fat and egg yolk fat of laying hens exposed to these compounds via feed. The estimated concentrations can be compared to the regulatory limits that have been defined by regulatory agencies in various countries.

For all congeners the same model structure was used, but parameter values were calibrated separately for each ndl-PCB congener. The model is available as a webtool application (<https://feedfoodtransfer.nl/>).

2 Model description

2.1 General overview

The transfer model used to estimate ndl-PCBs concentrations in egg yolk comprises two compartments representing a central compartment and a fat compartment (Fig 1). Intake of ndl-PCBs is modelled as a constant intake amount, A_i , of which a fraction (F_{abs}) is absorbed over the gut wall into the central compartment on a daily basis. Ndl-PCBs that have been absorbed by the central compartment can migrate to the fat compartment (q_c), and vice versa (q_f). Ndl-PCBs can leave the laying hen's body through two processes. The first is excretion to egg yolk fat (ϵy), with ϵ being the laying efficiency, and y being the excretion rate constant. The second is hepatic clearance (k).

For all congeners the same model structure was used as for the congener-specific transfer model for dioxins (PCDD/Fs and dl-PCBs) in laying hens, but parameter values were calibrated separately for each ndl-PCB congener (van Eijkeren et al., 2006; Notenboom et al., 2023).

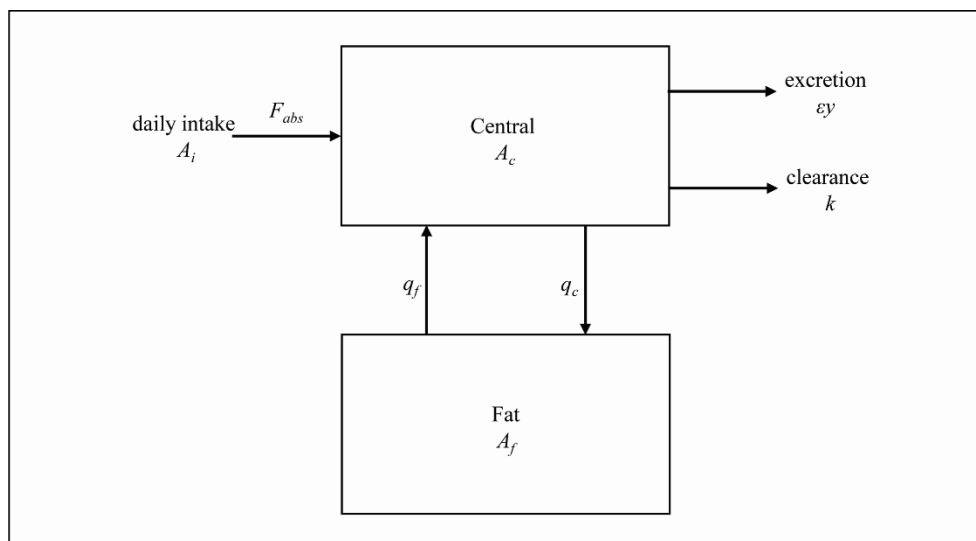


Figure 1. Two compartments comprised kinetic model for the ndl-PCB congeners in the laying hen (Adapted from Notenboom et al. 2023).

2.2 Model equations

The transfer model described in this report consists of a set of coupled ordinary differential equations (ODEs). These ODEs describe the distribution of ndl-PCBs between the central compartment and the fat compartment over time. For both compartments of the models, an ODE was formulated. Specifically, equations 1 and 2 describe the change in the amount of ndl-PCBs in the central compartment and the fat compartment, respectively.

$$\frac{dA_c(t)}{dt} = F_{abs}A_i - (q_c + \varepsilon y + k)A_c(t) + q_f A_f(t) \quad (1)$$

$$\frac{dA_f(t)}{dt} = q_c A_c(t) - q_f A_f(t) \quad (2)$$

$A_c(t)$ [pg]: Amount of substance in the central compartment at time t

$A_f(t)$ [pg]: Amount of substance in the fat compartment at time t

F_{abs} [-]: Absorption fraction

A_i [pg day⁻¹]: Daily intake amount of substance

q_c [day⁻¹]: Transfer rate constant from central compartment to fat compartment

q_f [day⁻¹]: Transfer rate constant from fat compartment to central compartment

ε [-]: Laying efficiency

y [day⁻¹]: Excretion rate constant from central compartment to egg yolk fat

k [day⁻¹]: Hepatic clearance rate constant

The transfer rate parameters used in equations 1 and 2 can be expressed as unknown model parameters (van Eijkeren et al., 2006):

$$q_c = \frac{Q}{P_c V_c} \quad (3)$$

$$q_f = \frac{Q}{P_f V_f} \quad (4)$$

$$y = \frac{P_{y,f} W_{y,f}}{P_c V_c} \quad (5)$$

$$k = \frac{CL}{P_c V_c} \quad (6)$$

Here, Q represents the compartment blood flow. V_c and V_f represent the volumes of the central and fat compartment, respectively. P_c and P_f represent the blood-body partition coefficient and the blood-fat partition coefficients, respectively. CL represents the hepatic clearance rate. $W_{y,f}$ is the amount of fat in the egg yolk and $P_{y,f}$ is the partition coefficient between the blood and the egg yolk fat.

The amount of ndl-PCB congeners in the body and fat compartment can be converted into concentrations by dividing the amount by the volume of the respective compartments, V_c and V_f .

Finally, the change in the amount of ndl-PCB congeners in eggs at a given time, $A_{yf}(t)$, can be calculated as follows:

$$\frac{dA_{yf}(t)}{dt} = \varepsilon y A_c(t) - A_{yf}(t) \quad (7)$$

2.3 Model assumptions

The following assumptions were made in the presented model:

- ndl-PCBs homogeneously distribute over the fat compartment.
- ndl-PCB concentrations measured in abdominal fat are representative of the ndl-PCB concentrations in the fat compartment.
- Hepatic sequestration was neglected
- The amount of fat in the egg yolk, $W_{y,f}$ is constant over time and can be measured.
- The laying hens are assumed to weigh 1840 grams (V_{total}). The sizes of the two compartments (central and fat) are calibrated.
- It is assumed that the hens get fed once a day with a constant amount of feed per day.
- The volume of the central compartment can be derived by taking the difference between the total volume and the volume of the fat compartment (which was calibrated (see section 2.5)).
- The density of the compartments is 1 g/cm³. The volume of the model compartments, V_c and V_f , are thus equal to the weights of the compartments (W_c and W_f).

2.4 Generic parameters

The remaining parameters (Table 1) are not specific to ndl-PCBs and can all be obtained from literature.

Table 1. Generic parameter values

Parameter	Value	Unit	Source
ϵ	0.9	day ⁻¹	Mean of exposure groups in Kan and Jonker-Den Rooyen (1978)
V_{total}	1840	cm ³	expert opinion
W_{egg}	60	g	Kan and Jonker-Den Rooyen (1978)
W_y	19.2	g	Gilbert (1971)
$W_{y,f}$	5.76	g	Gilbert (1971)

2.5 System-dependent parameters

As explained by van Eijkeren et al. (2006), the presented transfer model contains two parameters, q_c and q_f , that can be identified unconditionally from the available experimental data, whereas it contains four parameters, y , k , F_{abs} , and W_f , that are conditionally identifiable. The four conditionally identifiable parameters cannot be directly fitted to the data.

However, they can be determined in relation with each other (van Eijkeren et al., 2006):

$$c_1 = r = \epsilon y + k \quad (8)$$

$$c_2 = y F_{abs} \quad (9)$$

$$c_3 = \frac{F_{abs}}{W_f} \quad (10)$$

Here, parameters c_1 , c_2 , and c_3 can be fitted to the available experimental data. Although the four conditionally identifiable parameters cannot be directly fitted to the data and it is thus impossible to find a single value they should take on, it is possible to find the possible range of values they might take on. This can be done by defining boundary conditions on the parameter values. More specifically, the hepatic clearance, k , cannot be lower than 0 day^{-1} , whereas the absorption fraction, F_{abs} cannot exceed 1. If the model is fitted with the first boundary condition, i.e., $k \geq 0$, then it follows that $y \leq \frac{c_1}{\varepsilon}$, $F_{abs} \geq \frac{c_2}{y}$, and $W_f \geq \frac{F_{abs}}{c_3}$. Similarly, from the second boundary condition, i.e., $F_{abs} \leq 1$, it follows that $y \Rightarrow c_2$, $k \leq c_1 - \varepsilon c_2$ and $W_f \leq \frac{1}{c_3}$.

The true parameter values are thus mathematically bound to be within the boundaries described above. However, in order to find definitive parameter values for the transfer model, assumptions were necessary. Therefore, as a conservative estimate for the substance concentrations in egg yolk fat, an hepatic clearance of 0 was assumed, i.e., $k = 0$. From this assumption, it follows that $y = \frac{c_1}{\varepsilon}$, $F_{abs} = \frac{\varepsilon c_2}{c_1}$ and $W_f = \frac{\varepsilon c_2}{c_1 c_3}$. Based on these assumptions, the model parameters were calibrated using the experimental data reported by Hoogenboom et al. (2006) for each of the individual congeners. The calibrated parameters used in the transfer model are shown in Table 2.

Note that calibration of the parameters was not possible for PCB 52 and PCB 101. These compounds have been excluded from the current model.

Table 2. Calibrated parameter values used in the transfer model for the ndl-PCB congeners

Compound	q_c [day ⁻¹] Mass transfer rate from central compartment to fat compartment.*	q_f [day ⁻¹] Mass transfer rate from fat compartment to central compartment.*	F_{abs} [-] Absorption fraction. Calibrated.*	γ [day ⁻¹] Excretion rate constant to egg yolk fat	k [day ⁻¹] Hepatic clearance rate	V_f [g]
PCB 28	0.04	0.048	0.83	0.025	0	220
PCB 138	0.11	0.043	0.92	0.056	0	230
PCB 153	0.10	0.037	0.99	0.063	0	220
PCB 180	0.08	0.019	1	0.084	0	250

3 Software details

The transfer model simulations were developed and run using the R modelling language and using the deSolve package. Specifications on the programming packages are listed below:

Name software: R (tested with version 4.0.5)
Manufacturer: The R Foundation for Statistical Computing
Place of manufacture: online
Year of manufacture: 2021
Description: A programming language for statistical computing

Name software: DeSolve (tested with version 1.30)
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>

Name software: dplyr (tested with version 1.1.4)
Manufacturer: Hadley Wickham, Romain François, Lionel Henry, Kirill Müller, Davis Vaughan, Ryan Dickerson, Posit Software, PBC
Place of manufacture: online
Year of manufacture: 2023
Description: A fast, consistent tool for working with data frame like objects, both in memory and out of memory.
url: <https://cran.r-project.org/web/packages/dplyr/index.html>

4 Model applicability

The transfer model presented in this report can be used to simulate the transfer of ndl-PCBs from feed to body fat and egg yolk fat of laying hens. As such, the model enables comparison of the estimated concentration to regulatory limits of these food matrices. 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 2.

Exposure to various congeners was simulated for an exposure duration of 56 days. Concentrations of congeners in the contaminated feed are given in Table 3. Feed intake was 0.113 kg per day. After the 56 days of exposure to contaminated feed, an additional 200 days were simulated in which only clean feed was provided (i.e. feed not containing any ndl-PCB congeners).

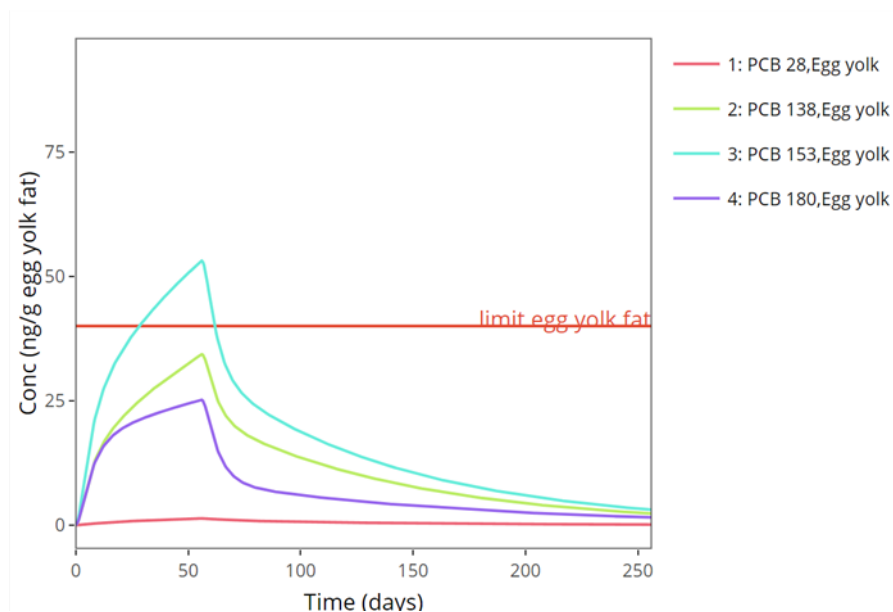


Figure 2 Simulated ndl-PCB concentrations in egg yolk of laying hens fed contaminated feed during 56 days followed by clean feed for 200 days. Laying hens were fed 0.113 kg dry feed per day.

Table 3 Congener concentrations in feed used to illustrate the simulation of the total TEQ concentration in egg yolk.

Congener	Concentration (ng kg ⁻¹ dry feed)
PCB 28	160
PCB 138	3300
PCB 153	4500
PCB 180	2000

5 References

Gilbert A (1971) The egg: its physical and chemical aspects. In "Physiology and Biochemistry of the Domestic Fowl" Vol. 3, eds. Bell, DJ, and Freeman, BM. Academic, New York.

Hoogenboom LAP, Kan CA, Zeilmaker MJ, van Eijkeren JCH, Traag WA (2006). Carry-over of dioxins and PCBs from feed and soil to eggs at low contamination levels. *Food Additives and Contaminants* 23:518–527. <https://doi.org/10.1080/02652030500512037>.

Kan CA and Jonker-Den Rooyen JC. (1978) Accumulation and depletion of some organochlorine pesticides in high-producing laying hens. *Journal of Agricultural and Food Chemistry*. 26(4): 935-940. <https://doi.org/10.1021/jf60218a007>.

Notenboom S, Punt A, Hoogenveen R, Zeilmaker MJ, Hoogenboom LAP, Bokkers BGH (2023) A congener-specific modelling approach for the transfer of polychlorinated dibenzo-p-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls from feed to eggs of laying hens, *Food Additives & Contaminants: Part A*, 40:1, 96-109. <https://doi.org/10.1080/19440049.2022.2137301>.

Van Eijkeren JCH, Zeilmaker MJ, Kan CA, Traag WA, Hoogenboom LAP (2006) A toxicokinetic model for the carry-over of dioxins and PCBs from feed and soil to eggs, *Food Additives & Contaminants*, 23:5, 509-517. <https://doi.org/10.1080/02652030500512045>.

Annex I: R-Code

The code below illustrates the basic implementation of the congener specific transfer model for ndl-PBCs in laying hens, v1.1. This code can be used freely and is provided "as is" without warranty of any kind. The National Institute of Public Health and the Environment (RIVM) expressly rejects all liability for the accuracy, completeness, or suitability of the information provided. Use of the information is entirely at your own risk.

Model code (ndlPCB-congener-laying-hen.R):

```
library(deSolve)

assign_parameters <- function(cpd) {
  #' Assign default parameters for the model
  #'
  #' @param cpd name of the compound for which the parameters are
  #' needed
  #'
  #' @return parameter vector

  inputParameters <- modelParameters |>
    mutate(
      contaminationLevel = input$contaminationLevel,
      dose = Fabs * contaminationLevel * 1000 * input$feedIntake
    )
  inputParameters[30, "dose"] <- sum(inputParameters$dose, na.rm =
  TRUE)

  # return all variables in this function's environment
  as.list(inputParameters |> filter(compound == cpd))
}

calculate_variables <- function(parameters) {
  #' Calculate derived parameters from the input parameters, e.g.
  #' scaling.
  #'
  #' @param parameters vector containing the model parameters
  #'
  #' @return parameter vector updated with derived parameters

  # calculate derived parameters from the input parameters, e.g.
  # scaling.
  with(parameters, {
    # return all variables in this function's environment
    as.list(sys.frame(sys.nframe()))
  }) # end with
}
```

```

# END!INITIAL

# DYNAMIC

# DERIVATIVE

derivative <- function(t, y, parameters, ...) {
  #' ODEs defining the model
  #'
  #' @param current time step
  #' @param y current state in a named list: `y <- c(D=dose, Ac=0,
  Af=0, AEgg=0)`
  #' @param parameters vector containing the model parameters
  #'
  #' @return derivative of each variable

  # define the derivatives of the model
  with(as.list(c(y, parameters)), {
    dD <- -D
    dAc <- D - (qcentral + k + e * yy) * Ac + qfat * Af
    dAf <- qcentral * Ac - qfat * Af
    dAEgg <- (e * yy) * Ac - AEgg

    return(list(c(dD, dAc, dAf, dAEgg),
      Cf = Af / Vf,
      Cegg = AEgg / 5.76
    ))
  })
}

run_model <- function(parameters) {
  #' Run model
  #'
  #' @param parameters vector containing the model parameters
  #'
  #' @return simulation results
  parameters <- calculate_variables(parameters)

  with(parameters, {
    tout <- seq(0, input$doseoff + input$tstop, by = 1)
    y0 <- c(D = dose, Ac = 0, Af = 0, AEgg = 0)
    dosing <- data.frame(
      var = c("D"),
      time = c(seq(0, input$doseoff, by = 1)), #
      value = c(dose),
      method = c("add")
    )
    solution <- ode(
      y = y0, times = tout, events = list(data = dosing),
      func = derivative, parms = parameters, method = "rk4"
    )
  })
}

```

```
    return(as.matrix(unclass(solution)))
  })
}
```

Running the model (example)

```
library(dplyr)
library(ggplot2)

source("ndIPCB-congener-laying-hen.R")

modelParameters <- read.csv("modelInputParameters.csv", header =
TRUE)

### User input ###
compounds <- c("C1", "C2", "C3", "C4")
contaminationLevel <- c("C1"=160, "C2"=3300, "C3"=4500, "C4"=2000) # ng /
kg
feedIntake <- 0.113 # kg
tstop <- 200 # days
tdoseoff <- 56 # days

### Run model ###
result <- list()
for (c in 1:length(compounds)){
  cpd <- compounds[c]
  input <- c(feedIntake = feedIntake, tstop = tstop, tdoseoff = tdoseoff,
contaminationLevel = list(contaminationLevel[[cpd]]))
  p <- assign_parameters(cpd)
  p <- calculate_variables(p)
  result[[c]] <- as.data.frame(run_model(p))
}
```

modellnputParameters.csv

compound,name	qcentral	qfat	e	yy	k	Fabs	Vf	Vc	Vtotal
C1,"1: PCB 28"	0.04	0.048	0.9	0.025	0	0.83	220	1620	1840
C2,"2: PCB 138"	0.11	0.043	0.9	0.056	0	0.92	230	1610	1840
C3,"3: PCB 153"	0.10	0.037	0.9	0.063	0	0.99	220	1620	1840
C4,"4: PCB 180"	0.08	0.019	0.9	0.084	0	1	250	1590	1840
