Supporting Information

Assessing global human exposure to T-2 toxin via poultry meat consumption using a lifetime physiologically based pharmacokinetic model

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Contents

1. Physiological parameters used in the PBPK model

Table S1. Physiological parameters in the PBPK model for T-2 toxin in chickens.

Parameter	Symbol	Mean	Source
Body weight (kg)	BW	1.3000	Calculated
Cardiac output (L/h/kg)	QCC	11.000	a
Blood flow rates for T-2 toxin (fraction of cardiac output, unitless)			
Kidney	QKC	0.250	b
Liver	QLC	0.350	b
Fat	QFC	0.015	b, c
Muscle	QMC	0.350	a
Rest of body	QRC	0.035	Calculated
Blood flow rates for T-2 triol (fraction of cardiac output, unitless)			
Kidney	QKC1	0.250	b
Liver	QLC1	0.350	b
Fat	QFC1	0.015	b, c
Muscle	QMC1	0.350	a
Rest of body	QRC1	0.035	Calculated
Tissue volumes for T-2 toxin (fraction of body weight, unitless)			
Blood	VbloodC	0.060	c
Kidney	VKC	0.0064	b
Liver	VLC	0.024	b
Fat	VFC	0.050	b
Muscle	VMC	0.400	b
Rest of body	VRC	0.4596	Calculated
Tissue volumes for T-2 triol (fraction of body weight, unitless)			
Blood	VbloodC1	0.060	c
Kidney	VKC1	0.0064	b
Liver	VLC1	0.024	b
Fat	VFC1	0.050	b
Muscle	VMC1	0.400	b
Rest of body	VRC1	0.4596	Calculated
Growth parameters for lifetime exposure (allometric relationships)			
Body weight at the beginning of the growth curve (kg)	BW_{BEGIN}	0.04	c
Body weight at the end of the growth curve (kg)	BW_{END}	2.04	c
Age at the beginning of the growth curve (days)	AGE_{BEGIN}	1	c
Age at the end of the growth curve (days)	AGE_{END}	35	c
Coefficient of the Gompertz equation for growth (day^{-1})	Bgomp	0.04455	c
Slope for the regression line of liver on body weight	$Slope_{Liver}$	0.8683	c
Intercept for the regression line of liver on body weight	$Intercept_{Liver}$	-3.673	c
Slope for the regression line of fat on body weight	$Slope_{Fat}$	1.118	c
Intercept for the regression line of fat on body weight	$Intercept_{Fat}$	-3.928	c
Slope for the regression line of leg muscle on body weight	$Slope_{LegMuscle}$	1.071	c
Intercept for the regression line of leg muscle weight on body weight	$Intercept_{LegMuscle}$	-1.965	c

Notes: a, b, c: the value was adopted from Yang et al. (2015)[1], Cortright et al. (2009)[2] and Henri et al. (2017)[3], respectively.

2 Chemical-specific parameters used in the PBPK model

Table S2. Chemical-specific Parameter in PBPK model.

Parameter	Symbol	Mean	Source
Oral absorption rate constants for T-2 toxin (/h)			
Gastric emptying rate constant	Kst	0.700	Estimated
Intestinal absorption rate constant	Ka	0.800	Estimated
Intestinal transit rate constant	Kint	2.000	Estimated
Bioavailability	Bioavail	0.177	Sun et al., 2015
IV infusion rate constants for T-2 toxin (h)	Timeiv	0.010	Estimated
Parameters of farming conditions for lifetime exposure			
Slope for the regression of feed intake on body weight (no unit)	a_feed	266.2	Henri et al., 2017
Intercept for the regression of feed intake on body weight (no unit)	b_feed	0.0005815	Henri et al., 2017
T-2 toxin concentration in feed (μg/kg of feed)	$Feed_{SupplLevel}$	250	EFSA, 2014
Time at beginning of the treatment (h)	TreatmentStart	0	Henri et al., 2017
Duration of the lighting period in a day (h)	LightingPeriod	20	Henri et al., 2017
Light is restored every 24 h (h)	PulseInterval	24	Henri et al., 2017
Tissue:plasma partition coefficient for T-2 toxin (unitless)			
Liver	PL	1.200	Calculated
Kidney	PK	1.000	Calculated
Muscle	PM	0.500	Calculated
Fat	PF	0.400	Calculated
Rest of body	PR	0.100	Calculated
Tissue:plasma partition coefficient for T-2 triol (unitless)			
Liver	PL1	0.500	Calculated
Kidney	PK1	1.000	Calculated
Muscle	PM1	0.100	Calculated
Fat	PF1	0.200	Calculated
Rest of body	PR1	0.100	Calculated
Hepatic metabolic rate [/(h*kg)]	KmC	250	Estimated
Fraction of T-2 toxin metabolized to triol (unitless)	Frac	0.900	Estimated
Percentage of plasma protein binding (unitless)			
T-2 toxin	PB	0.250	Estimated
T-2 triol	PB1	0.250	Estimated
Hepatic elimination rate constant (L/h/kg)			
T-2 toxin	KbileC	2.000	Estimated
T-2 triol	Kbile1C	2.000	Estimated
Urine elimination rate constant (L/h/kg)			
T-2 toxin	KurineC	0.050	Estimated
T-2 triol	Kurine1C	0.050	Estimated

Notes: Some parameters were estimated by fitting the PBPK model with the toxincokinetic data. These parameters were marked as “Estimated”. The tissue:plasma partition coefficients were calculated experimentally using the area under the concentration-time curve (AUC) method for T-2 toxin and T-2 triol. These parameters were marked as “Calculated”. Reference sources: Henri et al. (2017)[3]; Sun et al. (2015)[4]; EFSA (2014)[5].

3. Normalized sensitivity coefficients (NSCs) of highly sensitive parameters on selected plasma and tissue dose metrics following multiple oral gavage paradigms

Table S3. Normalized sensitivity coefficients (NSCs) of highly sensitive parameters on selected plasma and tissue dose metrics following multiple oral gavage paradigms.

Parameter[a]	Lifetime exposure at 0.25 mg/kg of feed				
	AUCCL1	AUCCK1	AUCCM1	AUCCF1	AUCCV1
QLC	1.55	1.55	1.55	1.55	1.55
QKC	1.10	1.10	1.10	1.10	1.10
QMC	1.55	1.55	1.55	1.55	1.55
$Slope_{Liver}$	-2.37	-2.37	-2.37	-2.37	-2.37
$Intercept_{Liver}$	-3.01	-3.01	-3.01	-3.01	-3.01
a_feed	1.00	1.00	1.00	1.00	1.00
b_feed	0.95	0.95	0.95	0.95	0.95
PL	0.83	0.83	0.83	0.83	0.83
PL1	1	-	-	-	-
PK1	-	1	-	-	-
PM1	-	-	1	-	-
PF1	-	-	-	1	-
KmC	0.83	0.83	0.83	0.83	0.83
Frac	1.00	1.00	1.00	1.00	1.00
KbileC	-0.80	-0.80	-0.80	-0.80	-0.80
Kbile1C	-0.96	-0.96	-0.96	-0.96	-0.96

- indicates a |NSC| smaller than 0.5.

[a] Only parameters with at least one absolute value of NSC greater than 0.5 are presented.

AUCCL1, AUCCK1, AUCCM1, AUCCF1 and AUCCV1 represent 24-h area under T-2 triol concentration curves in the liver, kidney, muscle, fat, and plasma, respectively.

4. Physiological and chemical-specific parameter distributions used in the Monte Carlo analysis

Table S4. Physiological and chemical-specific parameter distributions used in the Monte Carlo analysis.

Parameter	Mean	CV	SD	Lower bound	Upper bound	Distribution
QLC	0.35	0.300	0.105	1.442E-01	5.558E-01	Normal
QKC	0.25	0.300	0.075	1.030E-01	3.970E-01	Normal
QMC	0.35	0.300	0.105	1.442E-01	5.558E-01	Normal
Slopeliver	0.8683	0.300	0.260	3.577E-01	1.379E+00	Normal
Interceptliver	-3.673	0.300	-1.102	-1.513E+00	-5.833E+00	Normal
a_feed	266.2	0.100	26.620	2.140E+02	3.184E+02	Normal
b_feed	0.0005815	0.150	0.000	4.105E-04	7.525E-04	Normal
PL	1.2	0.200	0.240	7.982E-01	1.735E+00	Lognormal
PL1	0.5	0.200	0.100	3.326E-01	7.228E-01	Lognormal
PK1	1	0.200	0.200	6.651E-01	1.446E+00	Lognormal
PM1	0.1	0.200	0.020	6.651E-02	1.446E-01	Lognormal
PF1	0.2	0.200	0.040	1.330E-01	2.891E-01	Lognormal
KmC	250	0.200	50.000	1.663E+02	3.614E+02	Lognormal
Frac	0.9	0.200	0.180	5.986E-01	1.301E+00	Lognormal
KbileC	2	0.200	0.400	1.330E+00	2.891E+00	Lognormal
Kbile1C	2	0.200	0.400	1.330E+00	2.891E+00	Lognormal

Notes: QLC: fraction of cardiac output in liver; QKC: fraction of cardiac output in kidney; QMC: fraction of cardiac output in muscle; Slopeliver: Slope for the regression line of liver on body weight; Interceptliver: Intercept for the regression line of liver on body weight; a_feed: Slope for the regression of feed intake on body weight (no unit); b_feed: Intercept for the regression of feed intake on body weight (no unit); PL: Liver:plasma partition coefficient for T-2 toxin; PL1: Liver:plasma partition coefficient for T-2 triol; PK1: kidney:plasma partition coefficient for T-2 triol; PM1: muscle:plasma partition coefficient for T-2 triol; PF1: fat:plasma partition coefficient for T-2 triol; KmC: Hepatic metabolic rate; Frac: Fraction of T-2 toxin metabolized to triol; KbileC: hepatic elimination rate constant for T-2 toxin; Kbile1C: hepatic elimination rate constant for T-2 triol.

5. Poultry meat consumption factors from OECD in 2017

Table S5. Poultry meat consumption factors from OECD in 2017.

LOCATION	INDICATOR	SUBJECT	MEASURE	TIME	Value kg/capita	Value g/kg b.w. per day
SDN	MEATCONSUMP	POULTRY	KG_CAP	2017	0.000979	3.83E-05
ETH	MEATCONSUMP	POULTRY	KG_CAP	2017	0.534487	0.020919
NGA	MEATCONSUMP	POULTRY	KG_CAP	2017	0.906039	0.035461
BGD	MEATCONSUMP	POULTRY	KG_CAP	2017	1.23193	0.048216
TZA	MEATCONSUMP	POULTRY	KG_CAP	2017	1.468665	0.057482
MOZ	MEATCONSUMP	POULTRY	KG_CAP	2017	1.784754	0.069853
IND	MEATCONSUMP	POULTRY	KG_CAP	2017	1.957509	0.076615
SSA	MEATCONSUMP	POULTRY	KG_CAP	2017	2.131715	0.083433
ZMB	MEATCONSUMP	POULTRY	KG_CAP	2017	2.613563	0.102292
PAK	MEATCONSUMP	POULTRY	KG_CAP	2017	4.36643	0.170897
PRY	MEATCONSUMP	POULTRY	KG_CAP	2017	6.036024	0.236244
GHA	MEATCONSUMP	POULTRY	KG_CAP	2017	6.124008	0.239687
DZA	MEATCONSUMP	POULTRY	KG_CAP	2017	6.298612	0.246521
IDN	MEATCONSUMP	POULTRY	KG_CAP	2017	6.752108	0.26427
HTI	MEATCONSUMP	POULTRY	KG_CAP	2017	6.976766	0.273063
EGY	MEATCONSUMP	POULTRY	KG_CAP	2017	9.177057	0.35918
THA	MEATCONSUMP	POULTRY	KG_CAP	2017	10.02037	0.392187
BRICS	MEATCONSUMP	POULTRY	KG_CAP	2017	10.83287	0.423987
PHL	MEATCONSUMP	POULTRY	KG_CAP	2017	11.98357	0.469024
CHN	MEATCONSUMP	POULTRY	KG_CAP	2017	12.27283	0.480346
VNM	MEATCONSUMP	POULTRY	KG_CAP	2017	13.69358	0.535952
WLD	MEATCONSUMP	POULTRY	KG_CAP	2017	13.86014	0.542471
KAZ	MEATCONSUMP	POULTRY	KG_CAP	2017	13.98207	0.547243
JPN	MEATCONSUMP	POULTRY	KG_CAP	2017	14.27079	0.558543
URY	MEATCONSUMP	POULTRY	KG_CAP	2017	16.33332	0.639269
KOR	MEATCONSUMP	POULTRY	KG_CAP	2017	16.68396	0.652993
TUR	MEATCONSUMP	POULTRY	KG_CAP	2017	17.86443	0.699195
IRN	MEATCONSUMP	POULTRY	KG_CAP	2017	22.43066	0.877912
UKR	MEATCONSUMP	POULTRY	KG_CAP	2017	23.18318	0.907365
EU28	MEATCONSUMP	POULTRY	KG_CAP	2017	24.23944	0.948706
MEX	MEATCONSUMP	POULTRY	KG_CAP	2017	26.60106	1.041137
COL	MEATCONSUMP	POULTRY	KG_CAP	2017	27.29999	1.068493
RUS	MEATCONSUMP	POULTRY	KG_CAP	2017	28.67472	1.122298
OECD	MEATCONSUMP	POULTRY	KG_CAP	2017	30.19043	1.181622
ZAF	MEATCONSUMP	POULTRY	KG_CAP	2017	32.78601	1.28321
CHL	MEATCONSUMP	POULTRY	KG_CAP	2017	34.79571	1.361867
CAN	MEATCONSUMP	POULTRY	KG_CAP	2017	34.89126	1.365607
ARG	MEATCONSUMP	POULTRY	KG_CAP	2017	37.50803	1.468024
NZL	MEATCONSUMP	POULTRY	KG_CAP	2017	37.86065	1.481826
PER	MEATCONSUMP	POULTRY	KG_CAP	2017	38.24378	1.496821
BRA	MEATCONSUMP	POULTRY	KG_CAP	2017	39.90459	1.561823
MYS	MEATCONSUMP	POULTRY	KG_CAP	2017	41.69195	1.631779

AUS	MEATCONSUMP	POULTRY	KG_CAP	2017	44.46784	1.740424
SAU	MEATCONSUMP	POULTRY	KG_CAP	2017	44.66516	1.748147
USA	MEATCONSUMP	POULTRY	KG_CAP	2017	48.82849	1.911095
ISR	MEATCONSUMP	POULTRY	KG_CAP	2017	56.92912	2.228146

Note: the abbreviations in the column of location represent different countries. The country names refer to the OECD webpage (https://doi.org/10.1787/fa290fd0-en).

Calculation example: The poultry meat consumption value is 48.8 kilograms/capita for USA. The unit should be converted to g/kg b.w. per day. The following formula was used. The body weight for capita is 70kg. One year is equal to 365 days.

$$\frac{\frac{48.8 \times 1000}{70}}{365} = 1.911$$

6. Model calibration of single intravenous injection with plasma data

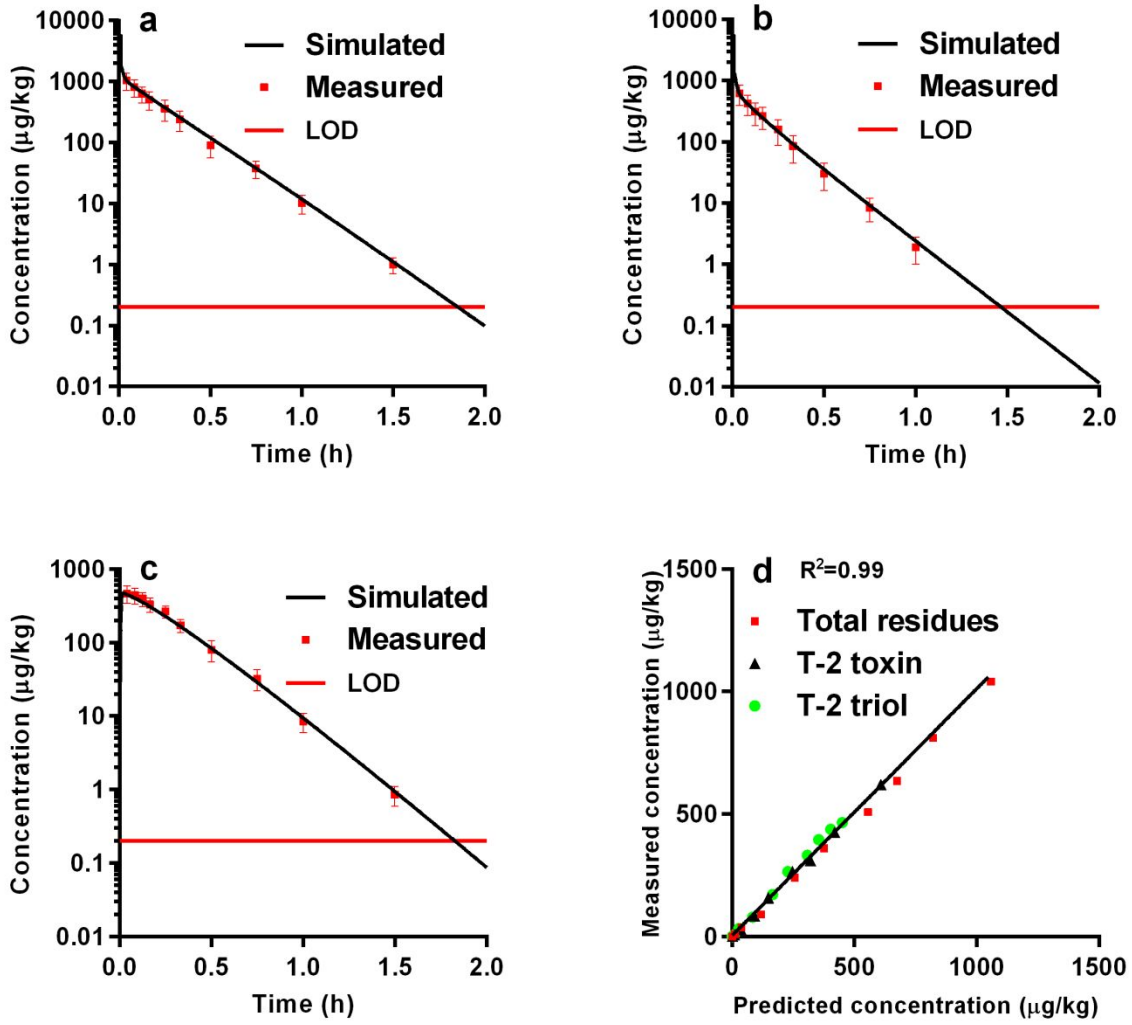

Figure S1. Model calibration of single intravenous injection with plasma data. Comparison of model predictions (solid line) and observed data (squares) for total residues (a), T-2 toxin (b), T-2 triol (c) of chickens exposed to T-2 toxin via single intravenous injection at 0.5 mg/kg. Result of regression analysis between model predictions and observed data is shown in d. The determination coefficient R^2 value is 0.99. Observed data are from data set 1 listed in Table 1.

7. Model calibration of multiple oral gavage with plasma data

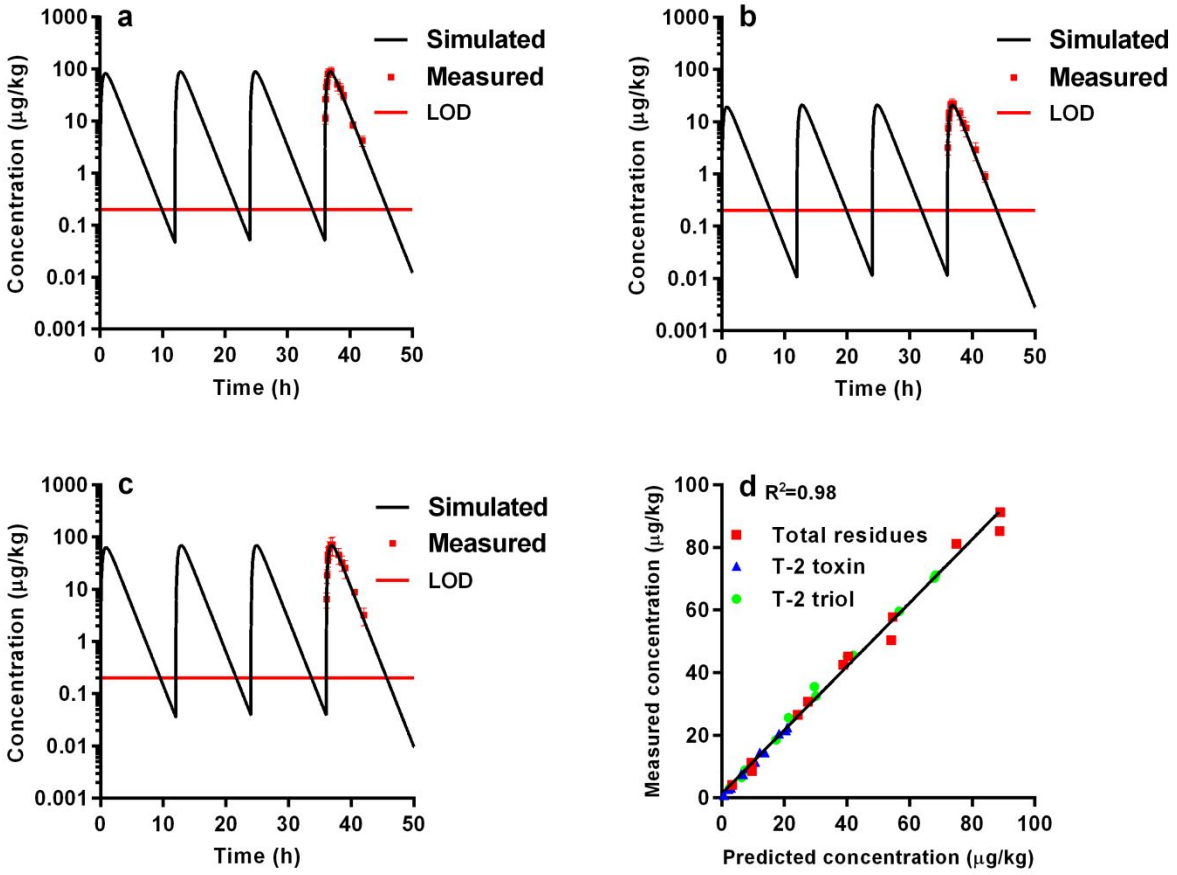

Figure S2. Model calibration of multiple oral gavage with plasma data. Comparison of model predictions (solid line) and observed data (squares) for total residues (a), T-2 toxin (b), and T-2 triol (c) of chickens exposed to T-2 toxin via multiple oral gavage at 2.0 mg/kg twice daily for 2 consecutive days. Result of regression analysis between model predictions and observed data is shown in d. The determination coefficient R^2 value is 0.98. Observed data are from data set 2 listed in Table 1.

8. Model calibration of multiple oral gavage with tissues and plasma data for T-2 toxin

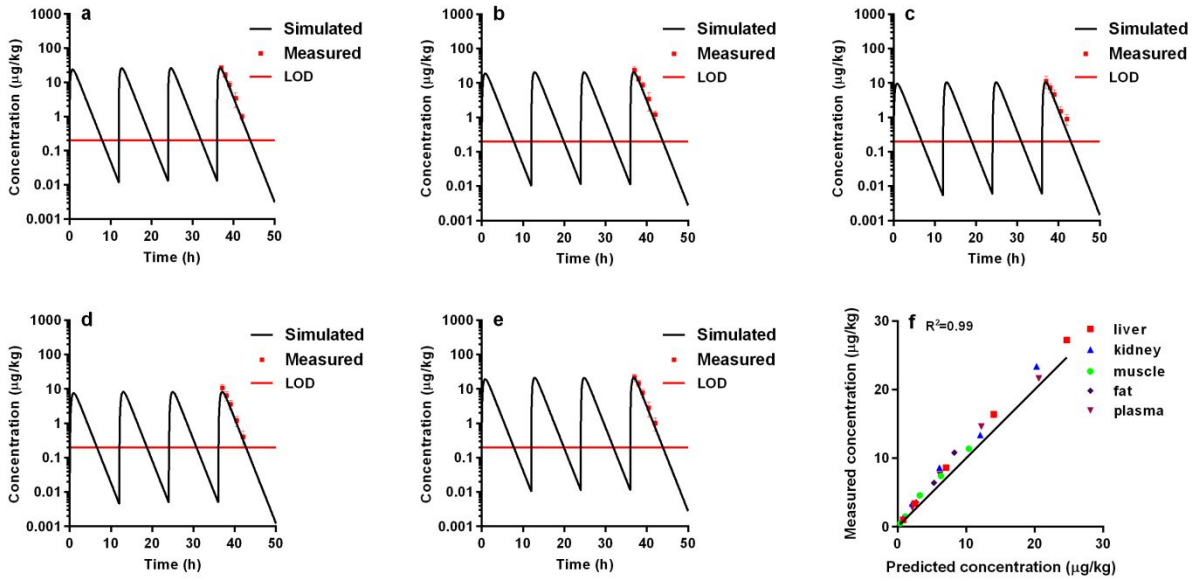

Figure S3. Model calibration of multiple oral gavage with tissues and plasma data for T-2 toxin. Comparison of model predictions (solid line) and observed data (squares) for T-2 toxin concentrations in liver (a), kidney (b), muscle (c), fat (d) and plasma (e) of chickens exposed to T-2 toxin via multiple oral gavage at 2.0 mg/kg twice daily for 2 consecutive days. Result of regression analysis between model predictions and observed data is shown in f. The determination coefficient R^2 value is 0.99. Observed data are from data set 3 listed in Table 1 collected as a part of the present study.

9. Model calibration of multiple oral gavage with tissues data for T-2 triol

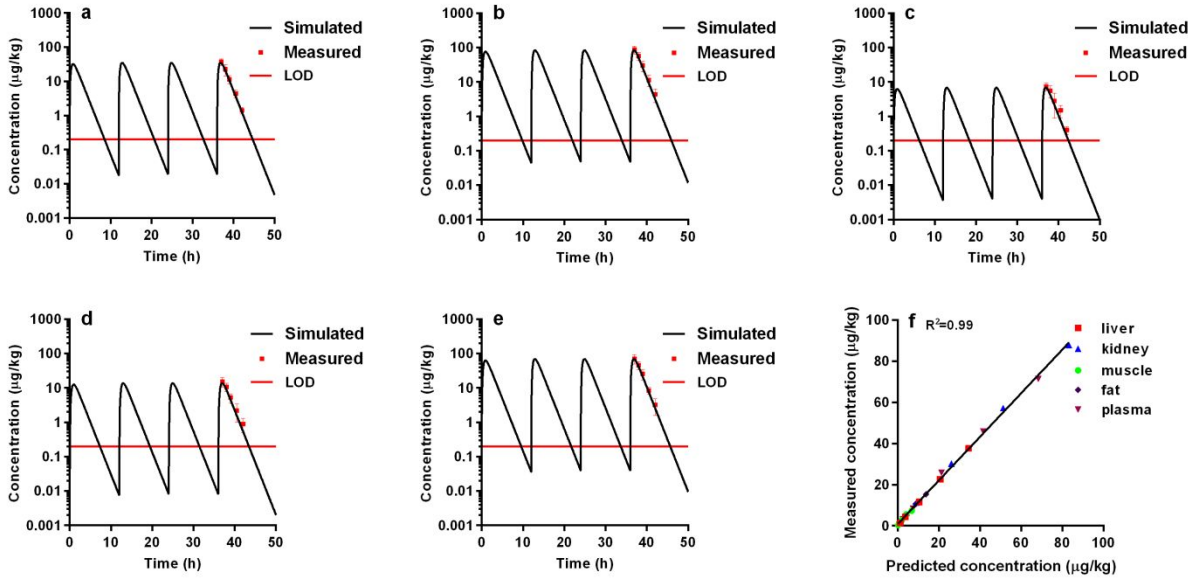

Figure S4. Model calibration of multiple oral gavage with tissues and plasma data for T-2 triol. Comparison of model predictions (solid line) and observed data (squares) for T-2 triol concentrations in liver (a), kidney (b), muscle (c), fat (d) and plasma (e) of chickens exposed to T-2 toxin via multiple oral gavage at 2.0 mg/kg twice daily for 2 consecutive days. Result of regression analysis between model predictions and observed data is shown in f. The determination coefficient R^2 value is 0.99. Observed data are from data set 3 listed in Table 1 collected as a part of the present study.

10. Model evaluation of single intravenous injection with plasma data from Osselaere et al. (2013)

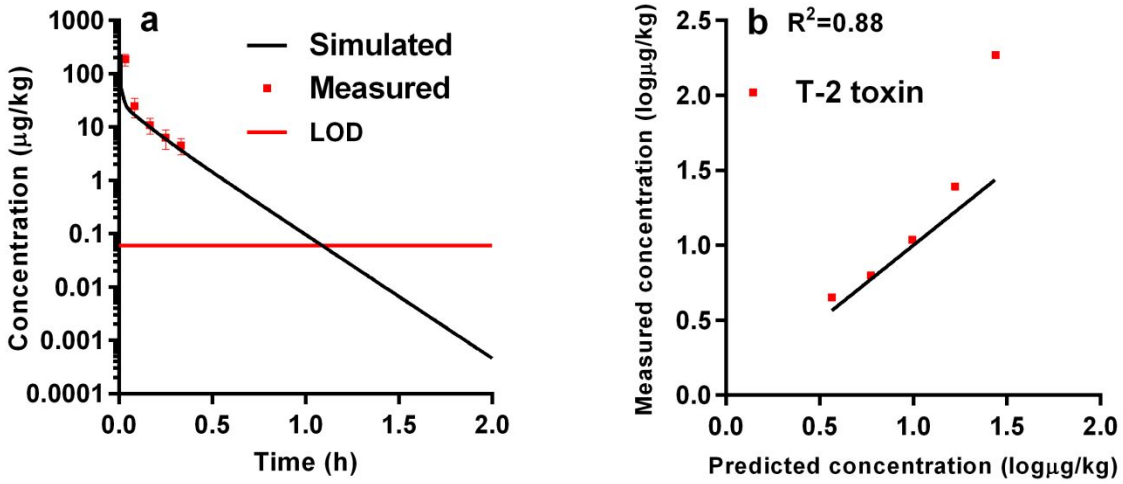

Figure S5. Model evaluation of single intravenous injection with plasma data from Osselaere et al. (2013)[6]**.** Comparison of model predictions (solid line) and observed data (squares) for T-2 toxin concentrations in plasma (a) of chickens exposed to T-2 toxin via single intravenous injection at 0.02 mg/kg. Result of regression analysis between model predictions and observed data is shown in b. The determination coefficient R^2 value is 0.88.

11. Model evaluation of single oral gavage with tissues data from Giroir et al. (1991)

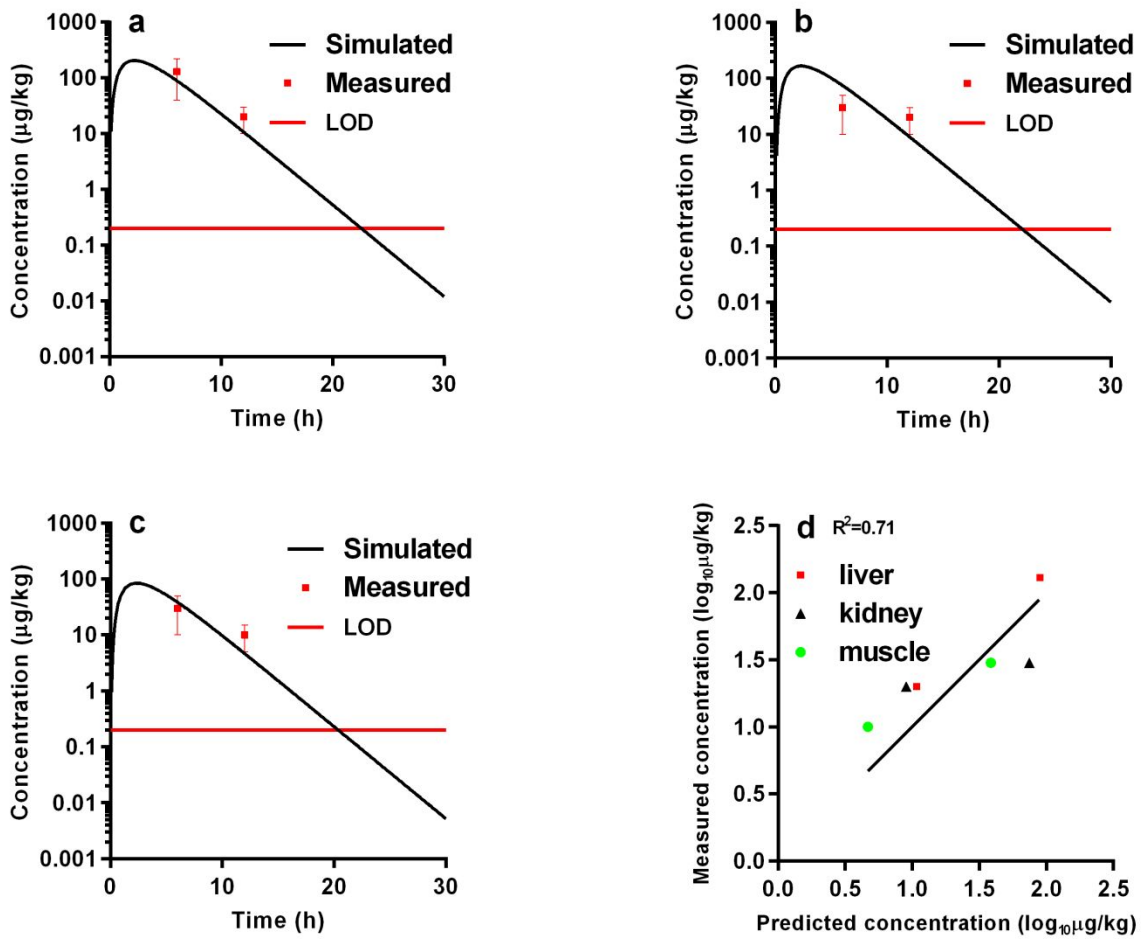

Figure S6. Model evaluation of single oral gavage with tissues data from Giroir et al. (1991)[7]. Comparison of model predictions (solid line) and observed data (squares) for total residue concentrations in liver (a), kidney (b) and muscle (c) of chickens exposed to T-2 toxin via single oral gavage at 0.5 mg/kg. Result of regression analysis between model predictions and observed data is shown in d. The determination coefficient R^2 value is 0.71.

12. Model evaluation of single oral gavage with tissue and plasma data from Chi et al. (1978)

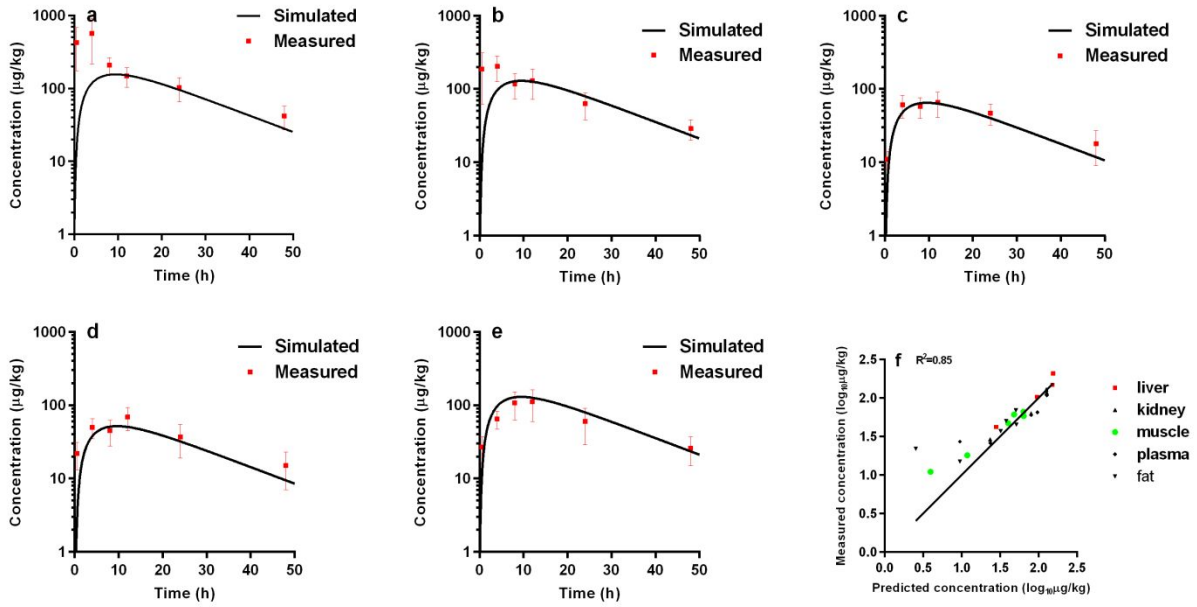

Figure S7. Model evaluation of single oral gavage with tissue and plasma data from Chi et al. (1978)[8]. Comparison of model predictions (solid line) and observed data (squares) for total residue concentrations in liver (a), kidney (b), muscle (c), fat (d) and plasma (e) of chickens exposed to T-2 toxin via single oral gavage at 0.5 mg/kg. Result of regression analysis between model predictions and observed data is shown in f. The determination coefficient R^2 value is 0.85.

13. Model simulation results of lifetime exposure at EFSA's indicative value for feed (2013/165/EU)

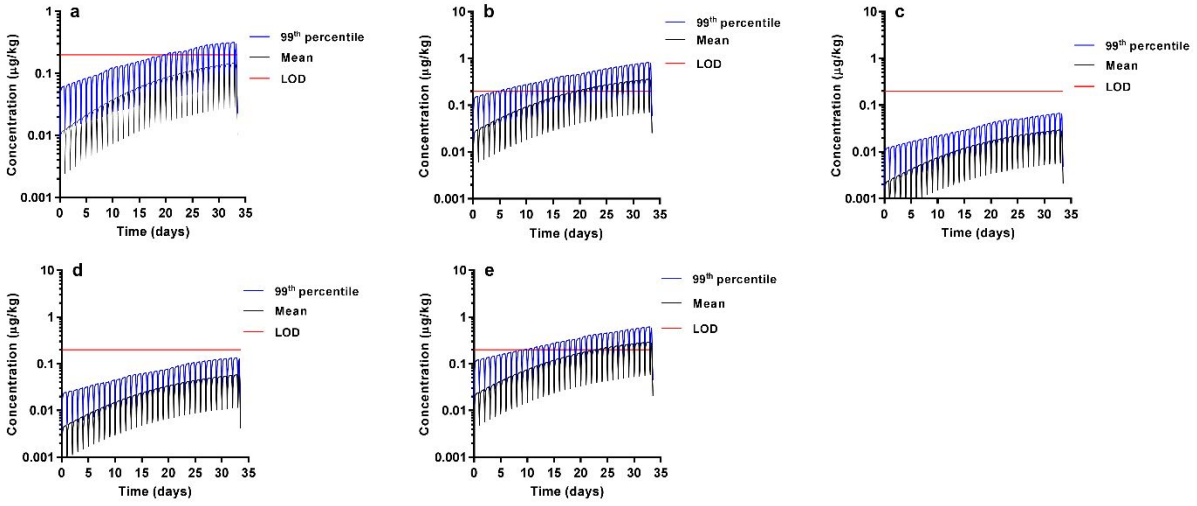

Figure S8. Model simulation results of lifetime exposure at EFSA's indicative value for feed (2013/165/EU). Model predictions (blue line, 99th percentile; black line, Mean) for T-2 triol concentrations in liver (a), kidney (b), muscle (c), fat (d) and plasma (e) of chickens exposed to T-2 toxin at guidance value of 0.25 mg/kg in feed for 33.25 consecutive days. LOD, limit of detection.

14. PBPK model code for an individual animal (MMD file)

```
METHOD RK4

STARTTIME = 0
STOPTIME = 50
DT = 0.0025
DTOUT = 0.001


; Physiological parameters
; Blood flow rates
QCC = 11.0 ; Cardiac output (L/h/kg) (Yang et al., 2015)

; Blood flow rates for T-2 toxin
QLC = 0.350 ; Fraction of blood flow to the liver (Cortright et al., 2009)
QKC = 0.250 ; Fraction of blood flow to the kidney (Cortright et al., 2009)
QFC = 0.015 ; Fraction of blood flow to the fat (Cortright et al., 2009; Henri et al., 2016)
QMC = 0.350 ; Fraction of blood flow to the muscle (Yang et al., 2015)
QRC = 0.035 ; Fraction of blood flow to the rest of body (QRC = 1-QLC-QKC-QFC-QMC)

; Blood flow rates for T-2 triol
QLC1 = 0.350 ; Fraction of blood flow to the liver (Cortright et al., 2009)
QKC1 = 0.250 ; Fraction of blood flow to the kidney (Cortright et al., 2009)
QFC1 = 0.015 ; Fraction of blood flow to the fat (Cortright et al., 2009; Henri et al., 2016)
QMC1 = 0.350 ; Fraction of blood flow to the muscle (Yang et al., 2015)
QRC1 = 0.035 ; Fraction of blood flow to the rest of body (QRC1 = 1-QLC1-QKC1-QFC1-
QMC1)

; Tissue volumes
BW = 1.3 ; Body weight (kg)

; Tissue volumes for T-2 toxin
VLC = 0.024 ; Fractional liver tissue (Cortright et al., 2009)
VKC = 0.0064 ; Fractional kidney tissue (Cortright et al., 2009)
VFC = 0.050 ; Fractional fat tissue (Cortright et al., 2009)
VMC = 0.400 ; Fractional muscle tissue (Cortright et al., 2009)
VRC = 0.4596 ; Fractional rest of body, VRC = 1-VLC-VKC-VFC-VMC-VbloodC
VbloodC = 0.060 ; Blood volume, fraction of BW (Henri et al., 2016)

; Tissue volumes for T-2 triol
VLC1 = 0.024 ; Fractional liver tissue (Cortright et al., 2009)
VKC1 = 0.0064 ; Fractional kidney tissue (Cortright et al., 2009)
VFC1 = 0.050 ; Fractional fat tissue (Cortright et al., 2009)
VMC1 = 0.400 ; Fractional muscle tissue (Cortright et al., 2009)
VRC1 = 0.4596 ; Fractional rest of body, VRC1 = 1-VLC1-VKC1-VFC1-VMC1-VbloodC1
VbloodC1 = 0.060 ; Blood volume, fraction of BW (Henri et al., 2016)

; Mass Transfer Parameters (Chemical-specific parameters)
; Chemical molecular weights and unit conversion factors
MW = 466.53 ; g/mol, T-2 toxin
```

```
MW1 = 382.45 ; g/mol, T-2 triol
MWmol = 2.13 ; umol/mg, T-2 toxin, from mg to umol
MWmg = 0.47 ; mg/umol, T-2 toxin, from umol to mg
MW1mol = 2.63 ; umol/mg, T-2 triol, from mg to umol
MW1mg = 0.38 ; mg/umol, T-2 triol, from umol to mg

; Partition coefficients for T-2 toxin, PC, unitless
PL = 1.2 ; Liver:plasma PC, estimated in the present study
PK = 1 ; Kidney:plasma PC, estimated in the present study
PF = 0.4 ; Fat:plasma PC, estimated in the present study
PM = 0.5 ; Muscle:plasma PC, estimated in the present study
PR = 0.1 ; Rest-of-body:plasma PC, estimated in the present study

; Partition coefficients for T-2 triol, PC, unitless
PL1 = 0.5 ; Liver:plasma PC, estimated in the present study
PK1 = 1 ; Kidney:plasma PC, estimated in the present study
PF1 = 0.2 ; Fat:plasma PC, estimated in the present study
PM1 = 0.1 ; Muscle:plasma PC, estimated in the present study
PR1 = 0.1 ; Rest-of-body:plasma PC, estimated in the present study

; Kinetic constants
; IV infusion rate constants for T-2 toxin
Timeiv = 0.01; IV injection/infusion time (h)

; Oral absorption and fecal elimination rate constants for T-2 toxin
Kst = 0.7 ; /h, gastric emptying rate constant, estimated in the present study
Ka = 0.8  /h, intestinal absorption rate constant, estimated in the present study
Kint = 2 ; /h, intestinal transit rate constant, estimated in the present study
Bioavail = 0.177 ; /%, Bioavailability of T-2 toxin, estimated in the present study

; Percentage of plasma protein binding (unitless), measured in the present study
PB = 0.25 ; Percentage of T-2 toxin bound to plasma proteins
PB1 = 0.25 ; Percentage of T-2 triol bound to plasma proteins
Free = 1-PB
Free1 = 1-PB1

; Metabolic rate constants
KmC = 250 ; /(h*kg), liver metabolic rate constant of T-2 toxin, estimated in the present study
Frac = 0.9 ; Unitless, fraction of T-2 toxin metabolized to T-2 triol, estimated in the present study

; Bile elimination rate constant
KbileC = 2 ; L/h/kg, for T-2 toxin, estimated in the present study
Kbile1C = 2 ; L/h/kg, for T-2 triol, measured in the present study

; Urine elimination rate constant
KurineC = 0.05 ; L/h/kg, for T-2 toxin, estimated in the present study
Kurine1C = 0.05 ; L/h/kg, for T-2 triol, measured in the present study

; Parameters for various exposure scenarios
PDOSEiv = 0.5 ; mg/kg
PDOSEoral = 0 ; mg/kg
```

```
; Cardiac output and blood flows to tissues (L/h)
QC = QCC*BW ; Cardiac output

; Cardiac output and blood flows to tissues for T-2 toxin (L/h)
QL = QLC*QC ; Liver
QK = QKC*QC ; Kidney
QF = QFC*QC ; Fat
QM = QMC*QC ; Muscle
QR = QRC*QC ; Rest of body

; Cardiac output and blood flows to tissues for T-2 triol (L/h)
QL1 = QLC1*QC ; Liver
QK1 = QKC1*QC ; Kidney
QF1 = QFC1*QC ; Fat
QM1 = QMC1*QC ; Muscle
QR1 = QRC1*QC ; Rest of body

; Tissue volumes (L)
; Tissue volumes for T-2 toxin (L)
VL = VLC*BW ; Liver
VK = VKC*BW ; Kidney
VF = VFC*BW ; Fat
VM = VMC*BW ; Muscle
VR = VRC*BW ; Rest of body
Vblood = VbloodC*BW ; Blood

; Tissue volumes for T-2 triol (L)
VL1 = VLC1*BW ; Liver
VK1 = VKC1*BW ; Kidney
VF1 = VFC1*BW ; Fat
VM1 = VMC1*BW ; Muscle
VR1 = VRC1*BW ; Rest of body
Vblood1 = VbloodC1*BW ; Blood

; Dosing amounts (mg converted to umol)
DOSEiv = PDOSEiv*BW*MWmol ; (umol)
DOSEoral = PDOSEoral*BW*MWmol ; (umol)

; Multiple dosing using the REPEAT/EXPOSURE function
tlen = 0.01 ; Length of oral gavage exposure (h/day)
tinterval = 12 ; Varied dependent on the exposure paradigm (h)
Tdoses = 4 ; times for multiple oral gavage
REPEAT[1..Tdoses] = SQUAREPULSE(0+(i-1)*tinterval, tlen)
Exposure = ARRAYSUM(REPEAT[*])

; Dosing, multiple oral gavage
RDOSEoral = (DOSEoral/tlen)*Exposure
RAST = RDOSEoral-Kst*AST
d/dt(AST) = RAST
init AST = 0
```

```
RAI = Kst*AST-Ka*AI-Kint*AI
Rcolon=Kint*AI
d/dt(Acolon) = Rcolon
init Acolon = 0
d/dt(AI) = RAI
init AI = 0
RAO=Ka*AI
d/dt(AAO) = RAO
init AAO = 0

; T-2 toxin iv injection to the venous
IVR = DOSEiv/Timeiv
RIV = IVR*(1.-step(1, Timeiv))
d/dt(Aiv) = Riv
init Aiv = 0

; Metabolic rate
Km = KmC*BW ; h-1

; Hepatic elimination rates
Kbile = KbileC*BW ; L/h, for T-2 toxin
Kbile1 = Kbile1C*BW ; L/h, for T-2 triol

; Urine elimination rates
Kurine = KurineC*BW ; L/h, for T-2 toxin
Kurine1 = Kurine1C*BW ; L/h, for T-2 triol

; Sub-model for T-2 toxin
; Blood compartment
CV = (QL*CVL+QK*CVK+QF*CVF+QM*CVM+QR*CVR+Riv)/QC
RA = QC*(CV-CAfree)
d/dt(AA) = RA
init AA = 0
CA = AA/Vblood
CAfree = CA*(1-PB)
CVmg = CV*MWmg
d/dt(AUCCV) = CV
init AUCCV = 0

; Liver compartment
RL = QL*(CAfree-CVL)+RAO-Rmet-Rbile
d/dt(AL) = RL
init AL = 0
CL = AL/VL
CVL = AL/(VL*PL)
CLmg=CL*MWmg
d/dt(AUCCL) = CL
init AUCCL = 0

; Metabolism of T-2 toxin in the liver compartment
Rmet=Km*CL*VL ; Total hepatic metabolic rate, umol/h
```

```
Rmet1=Rmet*Frac ; Hepatic metabolic rate to T-triol, umol/h
d/dt(Amet) = Rmet ; Amount of T-2 toxin that is metabolized in the liver, umol
init Amet = 0
d/dt(Amet1) = Rmet1 ; Amount of T-2 triol that is produced in the liver, umol
init Amet1 = 0

; Hepatic excretion of T-2 toxin
Rbile = Kbile*CVL
d/dt(Abile) = Rbile
init Abile = 0

; Kidney compartment
RK = QK*(CAfree-CVK)-Rurine
d/dt(AK) = RK
init AK = 0
CK = AK/VK
CVK = AK/(VK*PK)
CKmg=CK*MWmg

; Urinary excretion of OTC
Rurine = Kurine*CVK
d/dt(Aurine) = Rurine
init Aurine = 0

; Fat compartment
RF = QF*(CAfree-CVF)
d/dt(AF) = RF
init AF = 0
CF = AF/VF
CVF = AF/(VF*PF)
CFmg = CF*MWmg
d/dt(AUCCF) = CF
init AUCCF = 0

; Muscle compartment
RM = QM*(CAfree-CVM)
d/dt(AM) = RM
init AM = 0
CM = AM/VM
CVM = AM/(VM*PM)
CMmg=CM*MWmg
d/dt(AUCCM) = CM
init AUCCM = 0

; Rest-of-body compartment
RR = QR*(CAfree-CVR)
d/dt(AR) = RR
init AR = 0
CR = AR/VR
CVR = AR/(VR*PR)
CRmg=CR*MWmg
```

```
d/dt(AUCCR) = CR
init AUCCR = 0

; Mass balance for T-2 toxin
Qbal = QC-QL-QK-QF-QM-QR
Tmass = AA+AL+AK+AF+AM+AR+Abile+Amet+Aurine
Bal = AAO+Aiv-Tmass ; Mass balance

; Sub-model for T-2 triol
; Blood compartment
CV1 = (QL1*CVL1+QK1*CVK1+QF1*CVF1+QM1*CVM1+QR1*CVR1)/QC
RA1 = QC*(CV1-CA1free)
d/dt(AA1) = RA1
init AA1 = 0
CA1 = AA1/Vblood1
CV1mg=CV1*MW1mg
CA1free = CA1*(1-PB1)
d/dt(AUCCV1) = CV1
init AUCCV1 = 0

; Liver compartment
RL1 = QL1*(CA1free-CVL1)+Rmet1-Rbile1
d/dt(AL1) = RL1
init AL1 = 0
CL1 = AL1/VL1
CVL1 = AL1/(VL*PL1)
CL1mg=CL1*MW1mg
d/dt(AUCCL1) = CL1
init AUCCL1 = 0

; Hepatic excretion of T-2 triol
Rbile1 = Kbile1*CVL1
d/dt(Abile1) = Rbile1
init Abile1 = 0

; Kidney compartment
RK1 = QK1*(CA1free-CVK1)-Rurine1
d/dt(AK1) = RK1
init AK1 = 0
CK1 = AK1/VK1
CVK1 = AK1/(VK1*PK1)
CK1mg=CK1*MWmg

; Urinary excretion of T-2 toxin
Rurine1 = Kurine1*CVK1
d/dt(Aurine1) = Rurine1
init Aurine1 = 0

; Fat compartment
RF1 = QF1*(CA1free-CVF1)
d/dt(AF1) = RF1
```

```
init AF1 = 0
CF1 = AF1/VF1
CVF1 = AF1/(VF1*PF1)
CF1mg = CF1*MW1mg
d/dt(AUCCF1) = CF1
init AUCCF1 = 0

; Muscle compartment
RM1 = QM1*(CA1free-CVM1)
d/dt(AM1) = RM1
init AM1 = 0
CM1 = AM1/VM1
CVM1 = AM1/(VM1*PM1)
CM1mg=CM1*MW1mg
d/dt(AUCCM1) = CM1
init AUCCM1 = 0

; Rest-of-body compartment
RR1 = QR1*(CA1free-CVR1)
d/dt(AR1) = RR1
init AR1 = 0
CR1 = AR1/VR1
CVR1 = AR1/(VR1*PR1)
CR1mg = CR1*MW1mg
d/dt(AUCCR1) = CR1
init AUCCR1 = 0

; Mass balance for T-2 triol
Qbal1 = QC-QL1-QK1-QF1-QM1-QR1
Tmass1 = AA1+AL1+AK1+AF1+AM1+AR1+Abile1+Aurine1
Bal1 = Amet1-Tmass1 ; Mass balance

CVtotal = CVmg+CV1mg
CLtotal = CLmg+CL1mg
CKtotal = CKmg+CK1mg
CMtotal = CMmg+CM1mg
CFtotal = CFmg+CF1mg
```

15. Population PBPK model code

```
METHOD RK4

STARTTIME = 0
STOPTIME = 50
DT = 0.0025
DTOUT = 0.001

; Physiological parameters
; Blood flow rates
QCC = 11.0                                  ; Cardiac output (L/h/kg) (Yang et al., 2015)

; Blood flow rates for T-2 toxin
QLC = 0.350                                 ; Fraction of blood flow to the liver (Cortright
et al., 2009)
QKC = 0.250                                 ; Fraction of blood flow to the kidney
(Cortright et al., 2009)
QMC = 0.350                                 ; Fraction of blood flow to the muscle (Yang
et al., 2015)
QFC = 0.015                                 ; Fraction of blood flow to the fat (Cortright et
al., 2009; Henri et al., 2016)
QRC = 0.035                                 ; Fraction of blood flow to the rest of body
(QRC = 1-QLC-QKC-QFC-QMC)
QLC_sd = 0.105                              ; Standard deviation of QLC
QKC_sd = 0.075                              ; Standard deviation of QKC
QMC_sd = 0.105                              ; Standard deviation of QMC
init QLCm = Normal(QLC, QLC_sd)             ;  Generation of the QLCm based on normal
distribution
init QKCm = Normal(QKC, QKC_sd)             ;  Generation of the QKCm based on normal
distribution
init QMCm = Normal(QMC, QMC_sd)             ;  Generation of the QMCm based on normal
distribution
init QFCm = QFC
init QRCm = QRC
AdjustF1 = QLCm+QKCm+QMCm+QFC+QRC           ; Adjust factor for T-2 toxin to keep the sum
of blood flow fractions to 1
next QLCm = QLCm/AdjustF1                   ; Adjustment of QLCm based on the adjust
factor
next QKCm = QKCm/AdjustF1                   ; Adjustment of QKCm based on the adjust
factor
next QMCm = QMCm/AdjustF1                   ; Adjustment of QMCm based on the adjust
factor
next QFCm = QFCm/AdjustF1                   ; Adjustment of QFCm based on the adjust
factor
next QRCm = QRCm/AdjustF1                   ; Adjustment of QRCm based on the adjust
factor
limit QLCm >= 1.442E-01 ; limit the parameter values within the lower and upper bounds
limit QLCm <= 5.558E-01 ; limit the parameter values within the lower and upper bounds
limit QKCm >= 1.030E-01 ; limit the parameter values within the lower and upper bounds
limit QKCm <= 3.970E-01 ; limit the parameter values within the lower and upper bounds
```

```
limit QMCm >= 1.442E-01 ; limit the parameter values within the lower and upper bounds
limit QMCm <= 5.558E-01 ; limit the parameter values within the lower and upper bounds


; Blood flow rates for T-2 triol
QLC1 = 0.350                    ; Fraction of blood flow to the liver (Cortright et al., 2009)
QKC1 = 0.250                    ; Fraction of blood flow to the kidney (Cortright et al., 2009)
QFC1 = 0.015                    ; Fraction of blood flow to the fat (Cortright et al., 2009; Henri et
al., 2016)
QMC1 = 0.350                    ; Fraction of blood flow to the muscle (Yang et al., 2015)
QRC1 = 0.035                    ; Fraction of blood flow to the rest of body (QRC1 = 1-QLC1-
QKC1-QFC1-QMC1)
QLC1m = QLCm
QKC1m = QKCm
QMC1m = QMCm
QFC1m = QFCm
QRC1m = QRCm

; Tissue volumes
; Body weight growth during lifespan
AgeBegin = 1                    ; days, age at the beginning of the growth curve
AgeEnd = 35                     ; days, age at the end of the growth curve
BWBegin = 0.04                  ; kg, BW at the beginning of the growth curve
BWEnd = 2.04                    ; kg, BW at he end of the growth curve
Bgompertz = 0.0445516           ; growth rate of the gompertz function
hoursinaday = 24                ; conversion from a day to hours
BW=BWEnd*(BWEnd/BWBegin)**(-(EXP(-Bgompertz*(AgeEnd-AgeBegin))-EXP(-
Bgompertz*( (Time/hoursinaday) -AgeBegin)))/( -1+EXP(-Bgompertz*( AgeEnd-AgeBegin))))
                                ; Gompertz function, BW growth in function of time

; Tissue volumes for T-2 toxin
VKC = 0.0064                    ; Fractional kidney tissue (Cortright et al., 2009)
VbloodC = 0.060                 ; Blood volume, fraction of BW (Henri et al., 2016)

; Tissue volumes for T-2 triol
VKC1 = 0.0064                   ; Fractional kidney tissue (Cortright et al., 2009)
VbloodC1 = 0.060                ; Blood volume, fraction of BW (Henri et al., 2016)

; Mass Transfer Parameters (Chemical-specific parameters)
; Chemical molecular weights and unit conversion factors
MW = 466.53                     ; g/mol, T-2 toxin
MW1 = 382.45                    ; g/mol, T-2 triol
MWmol = 2.13                    ; umol/mg, T-2 toxin, from mg to umol
MWmg = 0.47                     ; mg/umol, T-2 toxin, from umol to mg
MW1mol = 2.63                   ; umol/mg, T-2 triol, from mg to umol
MW1mg = 0.38                    ; mg/umol, T-2 triol, from umol to mg

; Partition coefficients for T-2 toxin, PC, unitless
PL = 1.2                                                ; Liver:plasma PC, estimated in the
present study
```

```
PK = 1                                                    ; Kidney:plasma PC, estimated in the
present study
PF = 0.4                                                  ; Fat:plasma PC, estimated in the
present study
PM = 0.5                                                  ; Muscle:plasma PC, estimated in the
present study
PR = 0.1                                                  ; Rest-of-body:plasma PC, estimated in
the present study
PL_sd = 0.240                                             ; Standard deviation of PL
PL_ln = logn(PL^2/(PL_sd^2+PL^2)^0.5)                     ; Lognormal transformation of PL
values
PL_lnsd = (logn(1+PL_sd^2/PL^2))^0.5
init PLm = exp(Normal(PL_ln, PL_lnsd)) next PLm = PLm     ; Generation of PLm based on
lognormal distribution
limit PLm >= 7.982E-01 ; limit the parameter values within the lower and upper bounds
limit PLm <= 1.735E+00 ; limit the parameter values within the lower and upper bounds


; Partition coefficients for T-2 triol, PC, unitless
PL1 = 0.5                                                 ; Liver:plasma PC, estimated in the
present study
PK1 = 1                                                   ; Kidney:plasma PC, estimated in the
present study
PF1 = 0.2                                                 ; Fat:plasma PC, estimated in the
present study
PM1 = 0.1                                                 ; Muscle:plasma PC, estimated in the
present study
PR1 = 0.1                                                 ; Rest-of-body:plasma PC, estimated in
the present study
PL1_sd = 0.1                                              ; Standard deviation of PL1
PK1_sd = 0.2                                              ; Standard deviation of PK1
PM1_sd = 0.02                                             ; Standard deviation of PM1
PF1_sd = 0.04                                             ; Standard deviation of PF1
PL1_ln = logn(PL1^2/(PL1_sd^2+PL1^2)^0.5)                 ; Lognormal transformation of PL1
values
PL1_lnsd = (logn(1+PL1_sd^2/PL1^2))^0.5
PK1_ln = logn(PK1^2/(PK1_sd^2+PK1^2)^0.5)                 ; Lognormal transformation of PK1
values
PK1_lnsd = (logn(1+PK1_sd^2/PK1^2))^0.5
PM1_ln = logn(PM1^2/(PM1_sd^2+PM1^2)^0.5)                 ; Lognormal transformation of PM1
values
PM1_lnsd = (logn(1+PM1_sd^2/PM1^2))^0.5
PF1_ln = logn(PF1^2/(PF1_sd^2+PF1^2)^0.5)                 ; Lognormal transformation of PF1
values
PF1_lnsd = (logn(1+PF1_sd^2/PF1^2))^0.5
init PL1m = exp(Normal(PL1_ln, PL1_lnsd)) next PL1m = PL1m        ; Generation of
PL1m based on lognormal distribution
init PK1m = exp(Normal(PK1_ln, PK1_lnsd)) next PK1m = PK1m        ; Generation of
PK1m based on lognormal distribution
init PM1m = exp(Normal(PM1_ln, PM1_lnsd)) next PM1m = PM1m        ; Generation of
PM1m based on lognormal distribution
```

```
init PF1m = exp(Normal(PF1_ln, PF1_lnsd)) next PF1m = PF1m                ; Generation of
PF1m based on lognormal distribution
limit PL1m >= 3.326E-01 ; limit the parameter values within the lower and upper bounds
limit PL1m <= 7.228E-01 ; limit the parameter values within the lower and upper bounds
limit PK1m >= 6.651E-01 ; limit the parameter values within the lower and upper bounds
limit PK1m <= 1.446E+00 ; limit the parameter values within the lower and upper bounds
limit PM1m >= 6.651E-02 ; limit the parameter values within the lower and upper bounds
limit PM1m <= 1.446E-01 ; limit the parameter values within the lower and upper bounds
limit PF1m >= 1.330E-01 ; limit the parameter values within the lower and upper bounds
limit PF1m <= 2.891E-01 ; limit the parameter values within the lower and upper bounds


; Kinetic constants
; Oral absorption rate constants for T-2 toxin
Bioavail = 0.25              ; %, Bioavailability of T-2 toxin, estimated in the present study
K_abs = 3.85                 ; 1/h, constant of absorption (Henri et al., 2009)
K_crop = 0.5                 ; 1/h, constant of transit from crop to gut (Henri et al., 2016)
Tlag = 0.25                  ; h, delay time between input and output (Henri et al., 2016)

; Feed intake from breeders data
a_feed = 266.2                                  ; a_feed and b_feed were extracted from field
data (http://en.aviagen.com/ross-pm3/)
b_feed = 0.0005815                              ; a_feed and b_feed were extracted from field
data (http://en.aviagen.com/ross-pm3/)
a_feed_sd = 26.62                               ; Standard deviation of a_feed
b_feed_sd = 8.723E-05                           ; Standard deviation of b_feed
init a_feedm = Normal(a_feed, a_feed_sd) next a_feedm = a_feedm          ;  Generation of the
a_feedm based on normal distribution
init b_feedm = Normal(b_feed, b_feed_sd)  next b_feedm = b_feedm         ;  Generation of the
b_feedm based on normal distribution
feed_intake=(a_feedm*(1-exp(-b_feedm*BW)))
limit a_feedm >= 2.140E+02 ; limit the parameter values within the lower and upper bounds
limit a_feedm <= 3.184E+02 ; limit the parameter values within the lower and upper bounds
limit b_feedm >= 4.105E-04 ; limit the parameter values within the lower and upper bounds
limit b_feedm <= 7.525E-04 ; limit the parameter values within the lower and upper bounds


; T-2 toxin ingestion rate depending on feed intake, feed supplementation level
; the daily dose is distributed over the lighting period (it is assumed that chickens only eat when
light is switched on)
LightingPeriod=20                                                ; h lighting period
in a day (Henri, 2009)
feed_suppl_level=0.25*MWmol                                      ; umol of T-2
toxin per kg of feed, T-2 toxin supplementation level(2013/165/EU)
ingestion_rate=(feed_intake*feed_suppl_level)/LightingPeriod     ; umol of T-2
toxin per hour

; Events and Periods
PulseInterval=24.0                                               ; h, Interval
between two pulses of ingestion
```

```
TreatmentPeriod=6+33*hoursinaday                                    ; 33 days of
exposure plus 6 hours the day after
TreatmentStart = 0.0                                                ; h, beginning of
the treatment (start time of the first pulse)
SimulationPeriod=34*hoursinaday                                     ; h, lifespan


; Percentage of plasma protein binding (unitless), measured in the present study
PB = 0.25                   ; Percentage of T-2 toxin bound to plasma proteins
PB1 = 0.25                  ; Percentage of T-2 triol bound to plasma proteins
Free = 1-PB                 ; Percentage of T-2 toxin unbound to plasma proteins
Free1 = 1-PB1               ; Percentage of T-2 triol unbound to plasma proteins

; Metabolic rate constants
KmC = 250                   ; /(h*kg), liver metabolic rate constant of T-2 toxin, estimated in the
present study
Frac = 0.9                  ; Unitless, fraction of T-2 toxin metabolized to T-2 triol, estimated in the
present study
KmC_sd = 50                 ; Standard deviation of KmC
Frac_sd = 0.18              ; Standard deviation of Frac
KmC_ln = logn(KmC^2/(KmC_sd^2+KmC^2)^0.5)                           ; Lognormal
transformation of KmC
KmC_lnsd = (logn(1+KmC_sd^2/KmC^2))^0.5
Frac_ln = logn(Frac^2/(Frac_sd^2+Frac^2)^0.5)                       ; Lognormal
transformation of Frac
Frac_lnsd = (logn(1+Frac_sd^2/Frac^2))^0.5
init KmCm = exp(Normal(KmC_ln, KmC_lnsd)) next KmCm = KmCm          ;  Generation
of KmCm based on lognormal distribution
init Fracm = exp(Normal(Frac_ln, Frac_lnsd)) next Fracm = Fracm      ;  Generation
of Fracm based on lognormal distribution
limit KmCm >= 1.663E+02 ; limit the parameter values within the lower and upper bounds
limit KmCm <= 3.614E+02 ; limit the parameter values within the lower and upper bounds
limit Fracm >= 5.986E-01 ; limit the parameter values within the lower and upper bounds
limit Fracm <= 1.301E+00 ; limit the parameter values within the lower and upper bounds

; Bile elimination rate constant
KbileC = 2                  ; L/h/kg, for T-2 toxin, estimated in the present study
Kbile1C = 2                 ; L/h/kg, for T-2 triol, measured in the present study
KbileC_sd = 0.4             ; Standard deviation of KbileC
Kbile1C_sd = 0.4            ; Standard deviation of Kbile1C
KbileC_ln =
logn(KbileC^2/(KbileC_sd^2+KbileC^2)^0.5)                           ; Lognormal
transformation of KbileC
KbileC_lnsd = (logn(1+KbileC_sd^2/KbileC^2))^0.5
Kbile1C_ln =
logn(Kbile1C^2/(Kbile1C_sd^2+Kbile1C^2)^0.5)                        ; Lognormal
transformation of Kbile1C
Kbile1C_lnsd = (logn(1+Kbile1C_sd^2/Kbile1C^2))^0.5
init KbileCm = exp(Normal(KbileC_ln, KbileC_lnsd)) next KbileCm =
KbileCm                     ;  Generation of KbileCm based on lognormal distribution
```

```
init Kbile1Cm = exp(Normal(Kbile1C_ln, Kbile1C_lnsd)) next Kbile1Cm =
Kbile1Cm                    ;  Generation of Kbile1Cm based on lognormal distribution
limit KbileCm >= 1.330E+00 ; limit the parameter values within the lower and upper bounds
limit KbileCm <= 2.891E+00 ; limit the parameter values within the lower and upper bounds
limit Kbile1Cm >= 1.330E+00 ; limit the parameter values within the lower and upper bounds
limit Kbile1Cm <= 2.891E+00 ; limit the parameter values within the lower and upper bounds


; Urine elimination rate constant
KurineC = 0.05            ; L/h/kg, for T-2 toxin, estimated in the present study
Kurine1C = 0.05           ; L/h/kg, for T-2 triol, measured in the present study


; Cardiac output and blood flows to tissues (L/h)
QC = QCC*BW             ; Cardiac output

; Cardiac output and blood flows to tissues for T-2 toxin (L/h)
QL = QLCm*QC             ; Liver
QK = QKCm*QC             ; Kidney
QM = QMCm*QC             ; Muscle
QF = QFCm*QC             ; Fat
QR = QRCm*QC             ; Rest of body

; Cardiac output and blood flows to tissues for T-2 triol (L/h)
QL1 = QLC1m*QC         ; Liver
QK1 = QKC1m*QC         ; Kidney
QM1 = QMC1m*QC       ; Muscle
QF1 = QFC1m*QC           ; Fat
QR1 = QRC1m*QC         ; Rest of body

; Tissue volumes for T-2 toxin (L)
; Liver growth
slope_liver=0.8683                                                    ; slope of the growth curve
intercept_liver=-3.673                                                ; intercept of the growth
curve
slope_liver_sd = 0.26                                                 ; Standard deviation of
slope_liver
intercept_liver_sd = -1.102                                           ; Standard deviation of
intercept_liver
init slope_liverm = Normal(slope_liver, slope_liver_sd) next slope_liverm =
slope_liverm                ;  Generation of the slope_liverm based on normal distribution
init intercept_liverm = Normal(intercept_liver, intercept_liver_sd) next intercept_liverm =
intercept_liverm     ;  Generation of the intercept_liverm based on normal distribution
VL=exp(slope_liverm*LOGN(BW)+intercept_liverm)                        ; Liver growth in
function of BW
limit slope_liverm >= 3.577E-01 ; limit the parameter values within the lower and upper bounds
limit slope_liverm <= 1.379E+00 ; limit the parameter values within the lower and upper bounds
limit intercept_liverm >= -1.513E+00 ; limit the parameter values within the lower and upper
bounds
limit intercept_liverm <= -5.833E+00 ; limit the parameter values within the lower and upper
bounds
```

```
; Fat growth
slope_fat=1.188                                                    ; slope of the growth curve
intercept_fat=-3.9275                                              ; intercept of the growth curve
VF=exp(slope_fat*LOGN(BW)+intercept_fat)                           ; Fat growth in function of
BW

; Leg muscle growth
slope_LegMuscle=1.071                                              ; slope of the growth curve
intercept_LegMuscle=-1.965174944                                   ; intercept of the growth
curve
VM=exp(slope_legmuscle*LOGN(BW)+intercept_legmuscle)               ; Leg muscle  growth in
function of BW

VK = VKC*BW                                                        ; Kidney
Vblood = VbloodC*BW                                                ; Blood
VR = BW-(VL+VF+VM+VK+Vblood)                                       ; Rest of body

; Tissue volumes for T-2 triol (L)
VL1 = VL                                                           ; Liver
VK1 = VK                                                           ; Kidney
VF1 = VF                                                           ; Fat
VM1 = VM                                                           ; Muscle
Vblood1 = Vblood                                                   ; Blood
VR1 = VR                                                           ; Rest of body

; Feed intake, lifespan exposure
oral_ending = IF time > TreatmentPeriod Then 0 Else 1
oral_starting = IF time-TreatmentStart>=0 Then 1 Else 0
multiple_oral = IF MOD((time-TreatmentStart),PulseInterval)<=LightingPeriod Then 1 Else 0
R_CROP = ingestion_rate*multiple_oral*oral_starting*oral_ending-K_crop*A_CROP ; rate of
change of amount in crop
d/dt(A_CROP) = R_CROP
init A_CROP = 0

d/dt(A_GUT) = R_GUT
init A_GUT = 0
R_GUT = delay(K_crop*A_CROP,Tlag)-(K_abs*A_GUT)

RAO = K_abs*A_GUT
d/dt(AAO) = RAO
init AAO = 0

; Metabolic rate
Km = KmCm*BW ; h-1

; Hepatic elimination rates
Kbile = KbileCm*BW              ; L/h, for T-2 toxin
Kbile1 = Kbile1Cm*BW            ; L/h, for T-2 triol
```

```
; Urine elimination rates
Kurine = KurineC*BW          ; L/h, for T-2 toxin
Kurine1 = Kurine1C*BW        ; L/h, for T-2 triol

; Sub-model for T-2 toxin
; Blood compartment
CV = (QL*CVL+QK*CVK+QF*CVF+QM*CVM+QR*CVR)/QC
RA = QC*(CV-CAfree)
d/dt(AA) = RA
init AA = 0
CA = AA/Vblood
CAfree = CA*(1-PB)
CVmg = CV*MWmg
d/dt(AUCCV) = CV
init AUCCV = 0

; Liver compartment
RL = QL*(CAfree-CVL)+RAO-Rmet-Rbile
d/dt(AL) = RL
init AL = 0
CL = AL/VL
CVL = AL/(VL*PLm)
CLmg=CL*MWmg
d/dt(AUCCL) = CL
init AUCCL = 0

; Metabolism of T-2 toxin in the liver compartment
Rmet=Km*CL*VL                          ; Total hepatic metabolic rate, umol/h
Rmet1=Rmet*Frac                        ; Hepatic metabolic rate to T-triol, umol/h
d/dt(Amet) = Rmet                      ; Amount of T-2 toxin that is metabolized in the
liver, umol
init Amet = 0
d/dt(Amet1) = Rmet1                    ; Amount of T-2 triol that is produced in the liver,
umol
init Amet1 = 0

; Hepatic excretion of T-2 toxin
Rbile = Kbile*CVL
d/dt(Abile) = Rbile
init Abile = 0

; Kidney compartment
RK = QK*(CAfree-CVK)-Rurine
d/dt(AK) = RK
init AK = 0
CK = AK/VK
CVK = AK/(VK*PK)
CKmg=CK*MWmg

; Urinary excretion of OTC
```

```
Rurine = Kurine*CVK
d/dt(Aurine) = Rurine
init Aurine = 0

; Fat compartment
RF = QF*(CAfree-CVF)
d/dt(AF) = RF
init AF = 0
CF = AF/VF
CVF = AF/(VF*PF)
CFmg = CF*MWmg
d/dt(AUCCF) = CF
init AUCCF = 0

; Muscle compartment
RM = QM*(CAfree-CVM)
d/dt(AM) = RM
init AM = 0
CM = AM/VM
CVM = AM/(VM*PM)
CMmg=CM*MWmg
d/dt(AUCCM) = CM
init AUCCM = 0

; Rest-of-body compartment
RR = QR*(CAfree-CVR)
d/dt(AR) = RR
init AR = 0
CR = AR/VR
CVR = AR/(VR*PR)
CRmg=CR*MWmg
d/dt(AUCCR) = CR
init AUCCR = 0

; Mass balance for T-2 toxin
Qbal = QC-QL-QK-QF-QM-QR
Tmass = AA+AL+AK+AF+AM+AR+Abile+Amet+Aurine
Bal = AAO-Tmass ; Mass balance

; Sub-model for T-2 triol
; Blood compartment
CV1 = (QL1*CVL1+QK1*CVK1+QF1*CVF1+QM1*CVM1+QR1*CVR1)/QC
RA1 = QC*(CV1-CA1free)
d/dt(AA1) = RA1
init AA1 = 0
CA1 = AA1/Vblood1
CV1mg=CV1*MW1mg
CVtotal = CVmg+CV1mg
CA1free = CA1*(1-PB1)
d/dt(AUCCV1) = CV1
init AUCCV1 = 0
```

```
; Liver compartment
RL1 = QL1*(CA1free-CVL1)+Rmet1-Rbile1
d/dt(AL1) = RL1
init AL1 = 0
CL1 = AL1/VL1
CVL1 = AL1/(VL*PL1m)
CL1mg=CL1*MW1mg
CLtotal = CLmg+CL1mg
d/dt(AUCCL1) = CL1
init AUCCL1 = 0

; Hepatic excretion of T-2 triol
Rbile1 = Kbile1*CVL1
d/dt(Abile1) = Rbile1
init Abile1 = 0

; Kidney compartment
RK1 = QK1*(CA1free-CVK1)-Rurine1
d/dt(AK1) = RK1
init AK1 = 0
CK1 = AK1/VK1
CVK1 = AK1/(VK1*PK1m)
CK1mg=CK1*MWmg
CKtotal = CKmg+CK1mg

; Urinary excretion of T-2 toxin
Rurine1 = Kurine1*CVK1
d/dt(Aurine1) = Rurine1
init Aurine1 = 0

; Fat compartment
RF1 = QF1*(CA1free-CVF1)
d/dt(AF1) = RF1
init AF1 = 0
CF1 = AF1/VF1
CVF1 = AF1/(VF1*PF1m)
CF1mg = CF1*MW1mg
CFtotal = CFmg+CF1mg
d/dt(AUCCF1) = CF1
init AUCCF1 = 0

; Muscle compartment
RM1 = QM1*(CA1free-CVM1)
d/dt(AM1) = RM1
init AM1 = 0
CM1 = AM1/VM1
CVM1 = AM1/(VM1*PM1m)
CM1mg=CM1*MW1mg
CMtotal = CMmg+CM1mg
d/dt(AUCCM1) = CM1
```

```
init AUCCM1 = 0

; Rest-of-body compartment
RR1 = QR1*(CA1free-CVR1)
d/dt(AR1) = RR1
init AR1 = 0
CR1 = AR1/VR1
CVR1 = AR1/(VR1*PR1)
CR1mg = CR1*MW1mg
d/dt(AUCCR1) = CR1
init AUCCR1 = 0

; Mass balance for T-2 triol
Qbal1 = QC-QL1-QK1-QF1-QM1-QR1
Tmass1 = AA1+AL1+AK1+AF1+AM1+AR1+Abile1+Aurine1
Bal1 = Amet1-Tmass1 ; Mass balance
```

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