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 ........................................................................................................3
2 Chemical-specific parameters used in the PBPK model .................................................................................................4
3. Normalized sensitivity coefficients (NSCs) of highly sensitive parameters on selected plasma and tissue dose metrics following multiple oral gavage paradigms ..................................................................5
4. Physiological and chemical-specific parameter distributions used in the Monte Carlo analysis ........................................................................................................................................................................6
5. Poultry meat consumption factors from OECD in 2017 ...................................................................................................7
6. Model calibration of single intravenous injection with plasma data ..............................................................................9
7. Model calibration of multiple oral gavage with plasma data .........................................................................................10
8. Model calibration of multiple oral gavage with tissues and plasma data for T-2 toxin ...................................................11
9. Model calibration of multiple oral gavage with tissues data for T-2 triol ......................................................................12
10. Model evaluation of single intravenous injection with plasma data from Osselaere et al. (2013) .................................................................13
11. Model evaluation of single oral gavage with tissues data from Giroir et al. (1991) .......................................................14
12. Model evaluation of single oral gavage with tissue and plasma data from Chi et al. (1978) .................................................................15
13. Model simulation results of lifetime exposure at EFSA’s indicative value for feed (2013/165/EU) .................................................................16
14. PBPK model code for an individual animal (MMD file) .................................................................................................17
15. Population PBPK model code ......................................................................................................................................24
References ....................................................................................................................................................................34
1. Physiological parameters used in the PBPK model

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

Notes: a, b, c: the value was adopted from Yang et al. (2015)<sup>1</sup>, Cortright et al. (2009)<sup>2</sup> and Henri et al. (2017)<sup>3</sup>, respectively.
### Table S2. Chemical-specific Parameter in PBPK model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Mean</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption rate constants for T-2 toxin ((1/h))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying rate constant</td>
<td>Kst</td>
<td>0.700</td>
<td>Estimated</td>
</tr>
<tr>
<td>Intestinal absorption rate constant</td>
<td>Ka</td>
<td>0.800</td>
<td>Estimated</td>
</tr>
<tr>
<td>Intestinal transit rate constant</td>
<td>Kint</td>
<td>2.000</td>
<td>Estimated</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Bioavail</td>
<td>0.177</td>
<td>Sun et al., 2015</td>
</tr>
<tr>
<td>IV infusion rate constants for T-2 toxin ((h))</td>
<td>Timeiv</td>
<td>0.010</td>
<td>Estimated</td>
</tr>
<tr>
<td>Parameters of farming conditions for lifetime exposure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Slope for the regression of feed intake on body weight (no unit)</td>
<td>a_feed</td>
<td>266.2</td>
<td>Henri et al., 2017</td>
</tr>
<tr>
<td>Intercept for the regression of feed intake on body weight (no unit)</td>
<td>b_feed</td>
<td>0.0005815</td>
<td>Henri et al., 2017</td>
</tr>
<tr>
<td>T-2 toxin concentration in feed ((\mu g/kg) of feed)</td>
<td>Feed(_{\text{SupplLevel}})</td>
<td>250</td>
<td>EFSA, 2014</td>
</tr>
<tr>
<td>Time at beginning of the treatment ((h))</td>
<td>TreatmentStart</td>
<td>0</td>
<td>Henri et al., 2017</td>
</tr>
<tr>
<td>Duration of the lighting period in a day ((h))</td>
<td>LightingPeriod</td>
<td>20</td>
<td>Henri et al., 2017</td>
</tr>
<tr>
<td>Light is restored every 24 h ((h))</td>
<td>PulseInterval</td>
<td>24</td>
<td>Henri et al., 2017</td>
</tr>
<tr>
<td>Tissue:plasma partition coefficient for T-2 toxin (unitless)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>PL</td>
<td>1.200</td>
<td>Calculated</td>
</tr>
<tr>
<td>Kidney</td>
<td>PK</td>
<td>1.000</td>
<td>Calculated</td>
</tr>
<tr>
<td>Muscle</td>
<td>PM</td>
<td>0.500</td>
<td>Calculated</td>
</tr>
<tr>
<td>Fat</td>
<td>PF</td>
<td>0.400</td>
<td>Calculated</td>
</tr>
<tr>
<td>Rest of body</td>
<td>PR</td>
<td>0.100</td>
<td>Calculated</td>
</tr>
<tr>
<td>Tissue:plasma partition coefficient for T-2 triol (unitless)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>PL1</td>
<td>0.500</td>
<td>Calculated</td>
</tr>
<tr>
<td>Kidney</td>
<td>PK1</td>
<td>1.000</td>
<td>Calculated</td>
</tr>
<tr>
<td>Muscle</td>
<td>PM1</td>
<td>0.100</td>
<td>Calculated</td>
</tr>
<tr>
<td>Fat</td>
<td>PF1</td>
<td>0.200</td>
<td>Calculated</td>
</tr>
<tr>
<td>Rest of body</td>
<td>PR1</td>
<td>0.100</td>
<td>Calculated</td>
</tr>
<tr>
<td>Hepatic metabolic rate [/(h*kg)]</td>
<td>KmC</td>
<td>250</td>
<td>Estimated</td>
</tr>
<tr>
<td>Fraction of T-2 toxin metabolized to triol (unitless)</td>
<td>Frac</td>
<td>0.900</td>
<td>Estimated</td>
</tr>
<tr>
<td>Percentage of plasma protein binding (unitless)</td>
<td></td>
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<td></td>
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<tr>
<td>T-2 toxin</td>
<td>PB</td>
<td>0.250</td>
<td>Estimated</td>
</tr>
<tr>
<td>T-2 triol</td>
<td>PB1</td>
<td>0.250</td>
<td>Estimated</td>
</tr>
<tr>
<td>Hepatic elimination rate constant ((L/h/kg))</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>KbileC</td>
<td>2.000</td>
<td>Estimated</td>
</tr>
<tr>
<td>T-2 triol</td>
<td>Kbile1C</td>
<td>2.000</td>
<td>Estimated</td>
</tr>
<tr>
<td>Urine elimination rate constant ((L/h/kg))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>KurineC</td>
<td>0.050</td>
<td>Estimated</td>
</tr>
<tr>
<td>T-2 triol</td>
<td>Kurine1C</td>
<td>0.050</td>
<td>Estimated</td>
</tr>
</tbody>
</table>

Notes: Some parameters were estimated by fitting the PBPK model with the toxicokinetic 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); Sun et al. (2015); EFSA (2014).
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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUCCL1</th>
<th>AUCCK1</th>
<th>AUCCM1</th>
<th>AUCCF1</th>
<th>AUCCV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLC</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
</tr>
<tr>
<td>QKC</td>
<td>1.10</td>
<td>1.10</td>
<td>1.10</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>QMC</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
<td>1.55</td>
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<td>Intercept_Liver</td>
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<td>-3.01</td>
<td>-3.01</td>
<td>-3.01</td>
<td>-3.01</td>
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<tr>
<td>a_feed</td>
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<td>1.00</td>
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</tr>
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<td>b_feed</td>
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<td>0.95</td>
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<tr>
<td>PL</td>
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<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>PL1</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PK1</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td>PM1</td>
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<td>PF1</td>
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<td>-</td>
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<td>KmC</td>
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<tr>
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<td>Kbile1C</td>
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<td>-0.96</td>
<td>-0.96</td>
<td>-0.96</td>
<td>-0.96</td>
</tr>
</tbody>
</table>

- Indicates a \( |\text{NSC}| \) smaller than 0.5.

\textsuperscript{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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>CV</th>
<th>SD</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLC</td>
<td>0.35</td>
<td>0.300</td>
<td>0.105</td>
<td>1.442E-01</td>
<td>5.558E-01</td>
<td>Normal</td>
</tr>
<tr>
<td>QKC</td>
<td>0.25</td>
<td>0.300</td>
<td>0.075</td>
<td>1.030E-01</td>
<td>3.970E-01</td>
<td>Normal</td>
</tr>
<tr>
<td>QMC</td>
<td>0.35</td>
<td>0.300</td>
<td>0.105</td>
<td>1.442E-01</td>
<td>5.558E-01</td>
<td>Normal</td>
</tr>
<tr>
<td>Slope liver</td>
<td>0.8683</td>
<td>0.300</td>
<td>0.260</td>
<td>3.577E-01</td>
<td>1.379E+00</td>
<td>Normal</td>
</tr>
<tr>
<td>Intercept liver</td>
<td>-3.673</td>
<td>0.300</td>
<td>-1.102</td>
<td>-1.513E+00</td>
<td>-5.833E+00</td>
<td>Normal</td>
</tr>
<tr>
<td>a_feed</td>
<td>266.2</td>
<td>0.100</td>
<td>26.620</td>
<td>2.140E+02</td>
<td>3.184E+02</td>
<td>Normal</td>
</tr>
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<td>b_feed</td>
<td>0.0005815</td>
<td>0.150</td>
<td>0.000</td>
<td>4.105E-04</td>
<td>7.525E-04</td>
<td>Normal</td>
</tr>
<tr>
<td>PL</td>
<td>1.2</td>
<td>0.200</td>
<td>0.240</td>
<td>7.982E-01</td>
<td>1.735E+00</td>
<td>Lognormal</td>
</tr>
<tr>
<td>PL1</td>
<td>0.5</td>
<td>0.200</td>
<td>0.100</td>
<td>3.326E-01</td>
<td>7.228E-01</td>
<td>Lognormal</td>
</tr>
<tr>
<td>PK1</td>
<td>1</td>
<td>0.200</td>
<td>0.200</td>
<td>6.651E-01</td>
<td>1.446E+00</td>
<td>Lognormal</td>
</tr>
<tr>
<td>PM1</td>
<td>0.1</td>
<td>0.200</td>
<td>0.020</td>
<td>6.651E-02</td>
<td>1.446E-01</td>
<td>Lognormal</td>
</tr>
<tr>
<td>PF1</td>
<td>0.2</td>
<td>0.200</td>
<td>0.040</td>
<td>1.330E-01</td>
<td>2.891E-01</td>
<td>Lognormal</td>
</tr>
<tr>
<td>KmC</td>
<td>250</td>
<td>0.200</td>
<td>50.000</td>
<td>1.663E+02</td>
<td>3.614E+02</td>
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<td>0.400</td>
<td>1.330E+00</td>
<td>2.891E+00</td>
<td>Lognormal</td>
</tr>
<tr>
<td>Kbile1C</td>
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<td>0.200</td>
<td>0.400</td>
<td>1.330E+00</td>
<td>2.891E+00</td>
<td>Lognormal</td>
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</table>

Notes: QLC: fraction of cardiac output in liver; QKC: fraction of cardiac output in kidney; QMC: fraction of cardiac output in muscle; Slope liver: Slope for the regression line of liver on body weight; Intercept liver: 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.

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>INDICATOR</th>
<th>SUBJECT</th>
<th>MEASURE</th>
<th>TIME</th>
<th>Value kg/capita</th>
<th>Value g/kg b.w. per day</th>
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<tr>
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</table>

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.

$$\frac{48.8 \times 1000}{70} = \frac{1.911}{}$$
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). 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.
Figure S6. Model evaluation of single oral gavage with tissues data from Giroir et al. (1991)\textsuperscript{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). 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 tril 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(AUCCCL) = CL
init AUCCCL = 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

d/dt(Aurine) = Rurine
init Aurine = 0

; 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
\[ \frac{d}{dt}(AUCCR) = CR \]
\[ \text{init } AUCCR = 0 \]

; Mass balance for T-2 toxin
\[ Q_{\text{bal}} = QC - QL - QK - QF - QM - QR \]
\[ T_{\text{mass}} = AA + AL + AK + AF + AM + AR + Abile + Amet + Aurine \]
\[ Bal = AAO + Aiv - T_{\text{mass}} \]

; Sub-model for T-2 triol
; Blood compartment
\[ CV1 = \frac{QL1 \cdot CVL1 + QK1 \cdot CVK1 + QF1 \cdot CVF1 + QM1 \cdot CVM1 + QR1 \cdot CVR1}{QC} \]
\[ RA1 = QC \cdot (CV1 - CA1_{\text{free}}) \]
\[ \frac{d}{dt}(AA1) = RA1 \]
\[ \text{init } AA1 = 0 \]
\[ CA1 = AA1 / V_{\text{blood}1} \]
\[ CV1_{\text{mg}} = CV1 \cdot MW1_{\text{mg}} \]
\[ CA1_{\text{free}} = CA1 \cdot (1 - PB1) \]
\[ \frac{d}{dt}(AUCCV1) = CV1 \]
\[ \text{init } AUCCV1 = 0 \]

; Liver compartment
\[ RL1 = QL1 \cdot (CA1_{\text{free}} - CVL1) + R_{\text{met}1} - R_{\text{bile}1} \]
\[ \frac{d}{dt}(AL1) = RL1 \]
\[ \text{init } AL1 = 0 \]
\[ CL1 = AL1 / VL1 \]
\[ CVL1 = AL1 / (VL \cdot PL1) \]
\[ CL1_{\text{mg}} = CL1 \cdot MW1_{\text{mg}} \]
\[ \frac{d}{dt}(AUCCL1) = CL1 \]
\[ \text{init } AUCCL1 = 0 \]

; Hepatic excretion of T-2 triol
\[ R_{\text{bile}1} = Kbile1 \cdot CVL1 \]
\[ \frac{d}{dt}(Abile1) = R_{\text{bile}1} \]
\[ \text{init } Abile1 = 0 \]

; Kidney compartment
\[ RK1 = QK1 \cdot (CA1_{\text{free}} - CVK1) - R_{\text{urine}1} \]
\[ \frac{d}{dt}(AK1) = RK1 \]
\[ \text{init } AK1 = 0 \]
\[ CK1 = AK1 / VK1 \]
\[ CVK1 = AK1 / (VK1 \cdot PK1) \]
\[ CK1_{\text{mg}} = CK1 \cdot MW_{\text{mg}} \]

; Urinary excretion of T-2 toxin
\[ R_{\text{urine}1} = Kurine1 \cdot CVK1 \]
\[ \frac{d}{dt}(Aurine1) = R_{\text{urine}1} \]
\[ \text{init } Aurine1 = 0 \]

; Fat compartment
\[ RF1 = QF1 \cdot (CA1_{\text{free}} - CVF1) \]
\[ d/dt(AF1) = RF1 \]
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
(Qortright 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-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 the 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

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 \(K_{bile1C_m} = \exp(\text{Normal}(K_{bile1C\_ln}, K_{bile1C\_lnsd}))\) next \(K_{bile1C_m}\) = 
\(K_{bile1C_m}\) ; Generation of \(K_{bile1C_m}\) based on lognormal distribution

limit \(K_{bileC_m} \geq 1.330E+00\) ; limit the parameter values within the lower and upper bounds
limit \(K_{bileC_m} \leq 2.891E+00\) ; limit the parameter values within the lower and upper bounds
limit \(K_{bile1C_m} \geq 1.330E+00\) ; limit the parameter values within the lower and upper bounds
limit \(K_{bile1C_m} \leq 2.891E+00\) ; limit the parameter values within the lower and upper bounds

; Urine elimination rate constant
\(K_{urineC} = 0.05\) ; L/h/kg, for T-2 toxin, estimated in the present study
\(K_{urine1C} = 0.05\) ; L/h/kg, for T-2 triol, measured in the present study

; Cardiac output and blood flows to tissues (L/h)
\(Q_c = Q_{cc} \times BW\) ; Cardiac output

; Cardiac output and blood flows to tissues for T-2 toxin (L/h)
\(Q_L = Q_{LC_m} \times QC\) ; Liver
\(Q_K = Q_{KC_m} \times QC\) ; Kidney
\(Q_M = Q_{MC_m} \times QC\) ; Muscle
\(Q_F = Q_{FC_m} \times QC\) ; Fat
\(Q_R = Q_{RC_m} \times QC\) ; Rest of body

; Cardiac output and blood flows to tissues for T-2 triol (L/h)
\(Q_{L1} = Q_{LC1_m} \times QC\) ; Liver
\(Q_{K1} = Q_{KC1_m} \times QC\) ; Kidney
\(Q_{M1} = Q_{MC1_m} \times QC\) ; Muscle
\(Q_{F1} = Q_{FC1_m} \times QC\) ; Fat
\(Q_{R1} = Q_{RC1_m} \times QC\) ; Rest of body

; Tissue volumes for T-2 toxin (L)
; Liver growth
\(\text{slope\_liver} = 0.8683\) ; slope of the growth curve
\(\text{intercept\_liver} = -3.673\) ; intercept of the growth curve
\(\text{slope\_liver\_sd} = 0.26\) ; Standard deviation of \(\text{slope\_liver}\)
\(\text{intercept\_liver\_sd} = -1.102\) ; Standard deviation of \(\text{intercept\_liver}\)

init \(\text{slope\_liverm} = \text{Normal}(\text{slope\_liver}, \text{slope\_liver\_sd})\) next \(\text{slope\_liverm} = \text{slope\_liverm}\) ; Generation of the \(\text{slope\_liverm}\) based on normal distribution
init \(\text{intercept\_liverm} = \text{Normal}(\text{intercept\_liver}, \text{intercept\_liver\_sd})\) next \(\text{intercept\_liverm} = \text{intercept\_liverm}\) ; Generation of the \(\text{intercept\_liverm}\) based on normal distribution
\(V_L = \exp(\text{slope\_liverm} \times \logn(BW) + \text{intercept\_liverm})\) ; Liver growth in function of BW

limit \(\text{slope\_liverm} \geq 3.577E-01\) ; limit the parameter values within the lower and upper bounds
limit \(\text{slope\_liverm} \leq 1.379E+00\) ; limit the parameter values within the lower and upper bounds
limit \(\text{intercept\_liverm} \geq -1.513E+00\) ; limit the parameter values within the lower and upper bounds
limit \(\text{intercept\_liverm} \leq -5.833E+00\) ; 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)-urine

d/dt(AK) = RK
init AK = 0
CK = AK/VK
CVK = AK/(VK*PK)
CKmg=CK*MWmg

; Urinary excretion of OTC
Rurine = Kurine*CVK
\[ \frac{d}{dt}(\text{Aurine}) = \text{Rurine} \]
\[ \text{init Aurine} = 0 \]

; Fat compartment
RF = QF*(\text{CAfree-CVF})
\[ \frac{d}{dt}(\text{AF}) = \text{RF} \]
\[ \text{init AF} = 0 \]
CF = AF/VF
CVF = AF/(VF*PF)
CFmg = CF*MWmg
\[ \frac{d}{dt}(\text{AUCCF}) = \text{CF} \]
\[ \text{init AUCCF} = 0 \]

; Muscle compartment
RM = QM*(\text{CAfree-CVM})
\[ \frac{d}{dt}(\text{AM}) = \text{RM} \]
\[ \text{init AM} = 0 \]
CM = AM/VM
CVM = AM/(VM*PM)
CMmg=CM*MWmg
\[ \frac{d}{dt}(\text{AUCCM}) = \text{CM} \]
\[ \text{init AUCCM} = 0 \]

; Rest-of-body compartment
RR = QR*(\text{CAfree-CVR})
\[ \frac{d}{dt}(\text{AR}) = \text{RR} \]
\[ \text{init AR} = 0 \]
CR = AR/VR
CVR = AR/(VR*PR)
CRmg=CR*MWmg
\[ \frac{d}{dt}(\text{AUCCR}) = \text{CR} \]
\[ \text{init AUCCR} = 0 \]

; 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-\text{CA1free})
\[ \frac{d}{dt}(\text{AA1}) = \text{RA1} \]
\[ \text{init AA1} = 0 \]
CA1 = AA1/V\text{blood1}
CV1mg=CV1*MW1mg
CVtotal = CVmg+CV1mg
CA1free = CA1*(1-PB1)
\[ \frac{d}{dt}(\text{AUCCV1}) = \text{CV1} \]
\[ \text{init AUCCV1} = 0 \]
; Liver compartment
RL1 = QL1*(CA1free-CVL1)+Rmet1-Rbile1
\[ \frac{d}{dt}(AL1) = RL1 \]
init AL1 = 0
CL1 = AL1/VL1
CVL1 = AL1/(VL*PL1m)
CL1mg=CL1*MW1mg
CLtotal = CLmg+CL1mg
\[ \frac{d}{dt}(AUCCL1) = CL1 \]
init AUCCL1 = 0

; Hepatic excretion of T-2 triol
Rbile1 = Kbile1*CVL1
\[ \frac{d}{dt}(Abile1) = Rbile1 \]
init Abile1 = 0

; Kidney compartment
RK1 = QK1*(CA1free-CVK1)-Rurine1
\[ \frac{d}{dt}(AK1) = RK1 \]
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
\[ \frac{d}{dt}(Aurine1) = Rurine1 \]
init Aurine1 = 0

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

; Muscle compartment
RM1 = QM1*(CA1free-CVM1)
\[ \frac{d}{dt}(AM1) = RM1 \]
init AM1 = 0
CM1 = AM1/VM1
CVM1 = AM1/(VM1*PM1m)
CM1mg=CM1*MW1mg
CMtotal = CMmg+CM1mg
\[ \frac{d}{dt}(AUCCM1) = CM1 \]
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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