Supporting Information

APPLICATION OF BAYESIAN POPULATION PBPK MODELING AND MARKOV CHAIN MONTE CARLO SIMULATIONS TO PESTICIDE KINETICS STUDIES IN PROTECTED MARINE MAMMALS: DDT, DDE, DDD IN HARBOUR PORPOISES

Liesbeth Weijs1,2,*, Raymond SH Yang3, Krishna Das4, Adrian Covaci2, Ronny Blust1

1 - Department of Biology, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
2 - Toxicological Centre, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
3 - Quantitative and Computational Toxicology Group, Department of Environmental and Radiological Health Sciences, Colorado State University, 1680 Campus Delivery, Fort Collins, 80523, Colorado, USA
4 - Laboratory for Oceanology-MARE Center, University of Liège, 4000 Liège, Belgium

* - Corresponding author: Liesbeth Weijs, Department of Biology, University of Antwerp, Groenenborgerlaan 171, Building U, 5th Floor, 2020 Antwerp, Belgium.
E-mail: liesbeth.weijs@ua.ac.be
Phone: +32 3 265 35 41
Fax: +32 3 265 34 97

Supporting Information: Overview

Table S1. Parameters used for PBPK model calibration of male harbour porpoises.
Table S2. Results of the Morris sensitivity test
Figure S1. Results of the global sensitivity eFAST test on the concentration of p,p'-DDE
Figure S2. Results of the global sensitivity eFAST test on the concentration of p,p'-DDD
Figure S3. Results of the global sensitivity eFAST test on the concentration of p,p'-DDT
Codes of structural model (Berkeley Madonna)
List of references
Table S1. Parameters used for PBPK model calibration of male harbour porpoises. Table modified from Weijs et al. (2010b).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (BW; g)</td>
<td>1.387 x BS^{2.076}</td>
</tr>
<tr>
<td>Body Size (BS; cm)</td>
<td>142.4 x (1-0.3751 e^{-0.000068 x age})</td>
</tr>
<tr>
<td>Cardiac output (QC; L/hr)</td>
<td>(0.1017 x (BW/1000)^{0.9988}) x 60</td>
</tr>
<tr>
<td>Compartment mass (g):</td>
<td></td>
</tr>
<tr>
<td>blubber (V_F)</td>
<td>18.41 x BW^{0.607}</td>
</tr>
<tr>
<td>brain (V_B)</td>
<td>49.20 x BW^{0.211}</td>
</tr>
<tr>
<td>liver (V_L)</td>
<td>0.060 x BW^{0.932}</td>
</tr>
<tr>
<td>kidney (V_K)</td>
<td>0.002 x BW^{1.137}</td>
</tr>
<tr>
<td>muscle (V_R)</td>
<td>(0.99 x BW) - (V_F + V_B + V_L + V_K + V_{Blood})</td>
</tr>
<tr>
<td>blood (V_{Blood})</td>
<td>0.143 x BW</td>
</tr>
<tr>
<td>Density (DENS; g/L):</td>
<td></td>
</tr>
<tr>
<td>Blubber (F)</td>
<td>920</td>
</tr>
<tr>
<td>Brain (B)</td>
<td>1050</td>
</tr>
<tr>
<td>Liver (L)</td>
<td>1040</td>
</tr>
<tr>
<td>Kidney (K)</td>
<td>1050</td>
</tr>
<tr>
<td>Muscle (R)</td>
<td>1040</td>
</tr>
<tr>
<td>Blood</td>
<td>1068</td>
</tr>
<tr>
<td>Fractional blood flow (%)</td>
<td></td>
</tr>
<tr>
<td>to blubber (Q_{F}C)</td>
<td>5</td>
</tr>
<tr>
<td>to brain (Q_{B}C)</td>
<td>12</td>
</tr>
<tr>
<td>to liver (Q_{L}C)</td>
<td>25</td>
</tr>
<tr>
<td>to kidney (Q_{K}C)</td>
<td>19</td>
</tr>
<tr>
<td>to muscle (Q_{R}C)</td>
<td>100 - (Q_{F}C + Q_{B}C + Q_{L}C + Q_{K}C)</td>
</tr>
<tr>
<td>Lipid percentage (FATPERC; %)</td>
<td></td>
</tr>
<tr>
<td>blubber</td>
<td>92.85</td>
</tr>
<tr>
<td>liver</td>
<td>3.73</td>
</tr>
<tr>
<td>kidney</td>
<td>3.24</td>
</tr>
<tr>
<td>brain</td>
<td>11.49</td>
</tr>
<tr>
<td>blood</td>
<td>0.45</td>
</tr>
<tr>
<td>muscle</td>
<td>2.27</td>
</tr>
<tr>
<td>Daily consumption of milk (DCMILK; g/day)</td>
<td>540</td>
</tr>
<tr>
<td>Daily consumption of fish (DC; g/day)</td>
<td>0.123 x BW^{0.80}</td>
</tr>
</tbody>
</table>

a-correlations developed using existing data from male harbour porpoises from the literature; b-Von Bertalanffy age dependent growth-curves developed using existing data male harbour porpoises from the literature; c-Altman and Dittmer (1971); d-McLellan et al. (2002); e-Reed et al. (2000); f-Maruyama et al. (2002); g-Dolfinarium Harderwijk, The Netherlands, personal communication; h-Williams and Leggett (1989), Brown et al. (1997); i-Weijs et al. (2010a); k-Oftedal (1997); l-Innes et al. (1987)
Table S2. Results of the Morris sensitivity test. The influence of changes in all 49 parameters was tested on the concentration of DDT, DDE and DDD in the blood, respectively, as this medium connects all compartments. Parameter ranges were broad, but arbitrarily chosen. The Morris test yields two sensitivity measures for each parameter: \( \mu \) as an overall sensitivity measure and \( \sigma \) as an indication for a parameter interacting with other parameters or a parameter with a non-linear effect (McNally et al., 2011). According to the values of \( \mu \) and \( \sigma \), parameters were divided into 3 categories: I) very sensitive (values for \( \mu \) and \( \sigma \)), II) intermediate sensitive (values for \( \mu \) but \( \sigma \) values equal to zero) and III) not sensitive (extremely low values for \( \mu \) or \( \mu \) values equal to zero, \( \sigma \) values equal to zero). Parameters in grey were de-selected for the eFAST tests.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>cBlood_DDT</th>
<th>cBlood_DDE</th>
<th>cBlood_DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF_DDT</td>
<td>200 – 500</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>PR_DDT</td>
<td>0 – 15</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>PL_DDT</td>
<td>0.1 – 10</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PB_DDT</td>
<td>0.1 – 20</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PK_DDT</td>
<td>0.1 – 10</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PF_DDE</td>
<td>200 – 500</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>PR_DDE</td>
<td>0 – 15</td>
<td>II</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>PL_DDE</td>
<td>0.1 – 10</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>PB_DDE</td>
<td>0.1 – 20</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PK_DDE</td>
<td>0.1 – 10</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>PF_DDD</td>
<td>200 – 500</td>
<td>III</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>PR_DDD</td>
<td>0 – 15</td>
<td>II</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>PL_DDD</td>
<td>0.1 – 10</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PB_DDD</td>
<td>0.1 – 20</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>PK_DDD</td>
<td>0.1 – 10</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>TOTDIET_DDT</td>
<td>10 – 60</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>CMILK_DDT</td>
<td>400 – 12 000</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>DCMILK</td>
<td>300 – 800</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>IN_DIET_DDT</td>
<td>0.5 – 1</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>IN_MILK_DDT</td>
<td>0.5 – 1</td>
<td>II</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>TOTDIET_DDE</td>
<td>50 – 150</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>CMILK_DDE</td>
<td>2700 – 51 200</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>IN_DIET_DDE</td>
<td>0.5 – 1</td>
<td>III</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>IN_MILK_DDE</td>
<td>0.5 – 1</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>TOTDIET_DDD</td>
<td>30 – 120</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>CMILK_DDD</td>
<td>2300 – 33 000</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>IN_DIET_DDD</td>
<td>0.5 – 1</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>IN_MILK_DDD</td>
<td>0.5 – 1</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>QLC</td>
<td>0.2 – 0.4</td>
<td>II</td>
<td>III</td>
<td>II</td>
</tr>
<tr>
<td>QFC</td>
<td>0.01 – 0.2</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>QBC</td>
<td>0.1 – 0.2</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>QKC</td>
<td>0.1 – 0.2</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSFL</td>
<td>1000 – 1200</td>
<td>II</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>FATPERCL</td>
<td>0.01 – 0.2</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSF</td>
<td>850 – 1100</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>FATPERCF</td>
<td>0.65 – 0.99</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSB</td>
<td>1000 – 1200</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>FATPERCBB</td>
<td>0.03 – 0.3</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSK</td>
<td>1000 – 1200</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>FATPERCK</td>
<td>0.01 – 0.15</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSR</td>
<td>1000 – 1200</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>FATPERCR</td>
<td>0.01 – 0.15</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>DENSBlood</td>
<td>1000 – 1200</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>FATPERCBBlood</td>
<td>0.0001 – 0.01</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>ElimHL_DDT</td>
<td>0.0001 – 7</td>
<td>I</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>ElimHL_DDE</td>
<td>0.0001 – 7</td>
<td>III</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td>Partition Coefficient</td>
<td>Elimination Half-Life Value</td>
<td>TOTDIET</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>----------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>ElimHL_DDD</td>
<td>0.0001 – 7</td>
<td>III</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>PercDDT</td>
<td>0.1 – 0.7</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>PercDDD</td>
<td>0.01 – 0.5</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
</tbody>
</table>

P – partition coefficient between blood and tissue; ElimHL – elimination half-life value; TOTDIET – concentration in the fish diet; CMILK – concentration in the milk diet
Figure S1. Results of the global sensitivity eFAST test on the concentration of \( p,p' \)-DDE in blood over the entire lifetime of the animals. X-axis represents the age of the animals expressed in years. Y-axis represents the sensitivity coefficients.

* - PF_DDT, PL_DDT, PR_DDT, PK_DDT, PB_DDT, PF_DDD, PR_DDD, PB_DDD, CMILK_DDT, TOTDIET_DDT, TOTDIET_DDE, ElimHL_DDT, PercDDD, PercDDT
Figure S2. Results of the global sensitivity eFAST test on the concentration of $p,p'$-DDD in blood over the entire lifetime of the animals. X-axis represents the age of the animals expressed years. Y-axis represents the sensitivity coefficients.

* - PF_DDD, PL_DDT, PR_DDT, PK_DDT, PB_DDT, PR_DDD, PB_DDD, CMILK_DDE, CMILK_DDT, TOTDIET_DDT, TOTDIET_DDE, ElimHL_DDT, ElimHL_DDE, PercDDD, PercDDT
Figure S3. Results of the global sensitivity eFAST test on the concentration of \( p,p' \)-DDT in blood over the entire lifetime of the animals. X-axis represents the age of the animals expressed in years. Y-axis represents the sensitivity coefficients.
Codes of structural model (Berkeley Madonna)

NOTE: Parameters with the following description ‘UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS’ can be found in Table 3 in the main manuscript.

COMMENT: Codes of the structural and statistical model (AcslX/Libero) are available upon request to the corresponding author.

{---------------------PHYSIOLOGICAL PARAMETERS---------------------}

BW=1.387*BS**2.076  
{body weight (g), body size-dependent; Weijs et al., 2010b}

BS=142.4*(1-0.3751*exp(-0.000068*TIME))  
{body size or body length (cm), age-dependent; Weijs et al., 2010b}

VF=18.41*BW**0.607  
{Mass of fat (g), body weight-dependent; McLellan et al., 2002}

VFL=VF/DENSF  
{Volume of fat (L)}

DENSF=920  
{density of fat (human) =0.92 g/mL, Maruyama et al., 2002}

VB=49.20*BW**0.211  
{Mass of brain (g), body weight-dependent; McLellan et al., 2002}

VBL=VB/DENSB  
{Volume of brain (L)}

DENSB=1050  
{density of brain (human) =1.05 g/mL; Maruyama et al., 2002}

VL=0.060*BW**0.932  
{Mass of liver (g), body weight-dependent; McLellan et al., 2002}

VLL=VL/DENSL  
{Volume of liver (L)}

DENSL=1040  
{density of liver (human) =1.04 g/mL; Maruyama et al., 2002}

VK=0.002*BW**1.137  
{Mass of kidney (g), body weight-dependent; McLellan et al., 2002}

VKL=VK/DENSK  
{Volume of kidney (L)}

DENSK=1050  
{density of kidney (human) =1.05 g/mL; Maruyama et al., 2002}

VBlood=0.143*BW  
{Mass of blood (g), body weight dependent; Reed et al., 2000}

VBloodL=VBlood/DENSBlood  
{Volume of blood (L)}

DENSBlood=1068  
{density of blood (bottlenose dolphin; n=3; Harderwijk, personal communication)=1.068 g/mL}

VR=(0.99*BW)-VBlood-VK-VL-VB-VF  
{Compartment for 'Rest of the body'; under the assumption that 1% of the body is pharmacokinetically inactive}

VRL=VR/DENS R  
{Volume of rest of the body (muscle) (L)}

DENS R=1040  
{Density of muscle (human) =1.04 g/mL, Maruyama et al., 2002. The 'muscle' is the biggest part of 'the rest of the body' compartment and muscle parameters are therefore used when needed}

FATPERCF=0.9285
Fat percentage of various body parts:

- Fat percentage of blubber (FATPERCK): 0.0324
- Fat percentage of kidney (FATPERCL): 0.0373
- Fat percentage of liver (FATPERCB): 0.1149
- Fat percentage of brain (FATPERCBlood): 0.0045
- Fat percentage of muscle (FATPERCM): 0.1149

Cardiac output (QC):

\[ QC = 0.1017 \times (BW/1000)^{0.9988} \times 60 \]

Fat blood flow (QF) is a portion of the total blood flow to fat:

\[ QF = QFC \times QC \]

Liver blood flow (QL) is a portion of the total blood flow to liver:

\[ QL = QLC \times QC \]

Brain blood flow (QB) is a portion of the total blood flow to brain:

\[ QB = QBC \times QC \]

Kidney blood flow (QK) is a portion of the total blood flow to kidney:

\[ QK = QKC \times QC \]

Muscle blood flow (QR) is a portion of the total blood flow to muscle:

\[ QR = QRC \times QC \]

Fat/blood partition coefficient (PF_DDT): 331.0

Liver/blood partition coefficient (PL_DDT): 0.2

Brain/blood partition coefficient (PB_DDT): 1.5

Kidney/blood partition coefficient (PK_DDT): 0.9

Rest of the body/blood partition coefficient (PR_DDT): 3.5
PF_DDD=400.8
{"Fat/blood partition coefficient; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS}

PL_DDD=7.9
{"Liver/blood partition coefficient; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS}

PB_DDD=3.0
{"Brain/blood partition coefficient; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS}

PK_DDD=4.6
{"Kidney/blood partition coefficient; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS}

PR_DDD=15.0
{"Rest of the body/blood partition coefficient; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS; Rest of the body here is actually 'muscle'}

PF_DDE=450.0
{"Fat/blood partition coefficient; ATSDR, 2002}

PL_DDE=7.0
{"Liver/blood partition coefficient; ATSDR, 2002}

PB_DDE=6.0
{"Brain/blood partition coefficient; ATSDR, 2002}

PK_DDE=6.0
{"Kidney/blood partition coefficient; ATSDR, 2002}

PR_DDE=12.0
{"Rest of the body/blood partition coefficient; ATSDR, 2002; Rest of the body here is actually 'muscle'}

------------DOSING------------

TOTDIET_DDT=33.88
{"Tanabe et al., 1997a and b; unit ng/g ww (wet weight)"

IN_DDT=0.98
{"Assimilation efficiency; Thomas et al., 2005"

DC=(0.123*(BW/1000)**0.80)*1000
{"Daily Consumption (g/day) for porpoises according to Innes et al. (1987)"

DIET_DDT=(DC*IN_DDT*TOTDIET_DDT)/24
{"ng/hr; no unit*g/day*ng/g= ng/day divided by 24 hrs=ng/hr"

LACTATION_DDT=(IN_DDT*DCMILK*CMILK_DDT)/24
{"the same unit as DIET = ng/hr"

DCMILK=540
{"Daily Milk Consumption (g/day) for porpoises during lactation according to Oftedal (1997)"

FATPERMILK=0.2994
{"Fat percentage of milk of harbour porpoises; own analyses of Black Sea animals; Table 1 (main manuscript)"

CMILK_DDT=779.3
{"ng/g; own analyses of Black Sea animals"

DOSE_DDT=IF TIME<=2920 THEN LACTATION_DDT ELSE DIET_DDT
{"switch from milk-diet to fish-diet after 4 months (2920 hours) lactation"

TOTDIET_DDD=68.87
{"Tanabe et al., 1997a and b; unit ng/g ww (wet weight)"

IN_DDD=0.99
{"Assimilation efficiency; Thomas et al., 2005; this is a percentage }\}

DIET_DDD=(DC*IN_DDD*TOTDIET_DDD)/24
{"ng/hr; no unit*g/day*ng/g= ng/day divided by 24 hrs=ng/hr"

LACTATION_DDD=(IN_DDD*DCMILK*CMILK_DDD)/24
{"the same unit as DIET = ng/hr"

CMILK_DDD=1628.6
{"ng/g; own analyses of Black Sea animals"}
DOSE\_DDD=IF\ TIME\<=2920\ THEN\ LACTATION\_DDD\ ELSE\ DIET\_DDD
\{switch\ from\ milk-diet\ to\ fish-diet\ after\ 4\ months\ (2920\ hours)\ lactation\}\n
TOTD\_DDE=114.79
\{Tanabe\ et\ al.,\ 1997a\ and\ b;\ unit\ ng/g\ ww\ (wet\ weight)\}\nIN\_DDE=0.97
\{Assimilation\ efficiency;\ Thomas\ et\ al.,\ 2005;\ this\ is\ a\ percentage,\ so\ no\ unit\}\nDIET\_DDE=\(\text{DC}\times\text{IN}\_DDE\times\text{TOTD}\_DDE\)/24
\{ng/hr\ /\ no\ unit\ g/day\ g\ /\ ng/day\ divided\ by\ 24\ hrs=ng/hr\}\nLACTATION\_DDE=\(\text{IN}\_DDE\times\text{DCMILK}\times\text{CMILK}\_DDE\)/24
\{the\ same\ unit\ as\ DIET=ng/hr\}\nCMILK\_DDE=2011.7
\{ng/g;\ own\ analyses\ of\ Black\ Sea\ animals\}\nDOSE\_DDD=IF\ TIME\<=2920\ THEN\ LACTATION\_DDD\ ELSE\ DIET\_DDD
\{switch\ from\ milk-diet\ to\ fish-diet\ after\ 4\ months\ (2920\ hours)\ lactation\}\n
\{---------MASS-BALANCE\ EQUATIONS\ DDT---------\}\n
\text{AF}\_DDT'=\text{QF}\times(\text{CBlood}\_DDT-\text{CVF}\_DDT)
\text{CVF}\_DDT=\text{CF}\_DDT/\text{PF}\_DDT
\text{CF}\_DDT=\text{AF}\_DDT/\text{VFL}
\text{CFG}\_DDT=\text{CF}\_DDT/(\text{DENSF}\times\text{FATPERCF})
\text{init}\ \text{AF}\_DDT=\text{CFoetus}\_DDT\times\text{DENSF}\times\text{VFL}
\text{CFoetus}\_DDT=918.8

\text{AR}\_DDT'=\text{QR}\times(\text{CBlood}\_DDT-\text{CVR}\_DDT)
\text{CVR}\_DDT=\text{CR}\_DDT/\text{PR}\_DDT
\text{CR}\_DDT=\text{AR}\_DDT/\text{VRL}
\text{CRG}\_DDT=\text{CR}\_DDT/(\text{DENSR}\times\text{FATPERCR})
\text{init}\ \text{AR}\_DDT=\text{CFoetus}\_R\_DDT\times\text{DENSR}\times\text{VRL}
\text{CFoetus}\_R\_DDT=0.000001

\text{AL}\_DDT'=\text{QL}\times(\text{CBlood}\_DDT-\text{CVL}\_DDT)-\text{HepMet}\_DDT+\text{DOSE}\_DDT)
\text{CVL}\_DDT=\text{CL}\_DDT/\text{PL}\_DDT
\text{CL}\_DDT=\text{AL}\_DDT/\text{VLL}
\text{CLG}\_DDT=\text{CL}\_DDT/(\text{DENSL}\times\text{FATPERCL})
\text{init}\ \text{AL}\_DDT=\text{CFoetus}\_L\_DDT\times\text{DENSL}\times\text{VLL}
\text{CFoetus}\_L\_DDT=0.000001

\text{CLint}\_DDT=0.06315
\{Biotransformation\ in\ liver;\ calculated\ according\ Verner\ et\ al.\ (2009)\ using\ an\ elimination\ half\ life\ of\ 4.8\ years;\ UPDATED\ WITH\ BAYESIAN\ APPROACH\ AND\ MCMC\ SIMULATIONS\}\n\text{Eh}\_DDT=(\text{CLint}\_DDT\times\text{VLL})/(\text{CLint}\_DDT\times\text{VLL}\times\text{QL})
\text{HepMet}\_DDT=\text{QL}\times\text{Eh}\_DDT\times\text{CBlood}\_DDT

\text{AK}\_DDT'=\text{QK}\times(\text{CBlood}\_DDT-\text{CVK}\_DDT)
\text{CVK}\_DDT=\text{CK}\_DDT/\text{PK}\_DDT
\text{CK}\_DDT=\text{AK}\_DDT/\text{VKL}
\text{CKG}\_DDT=\text{CK}\_DDT/(\text{DENSK}\times\text{FATPERCK})
\text{init}\ \text{AK}\_DDT=\text{CFoetus}\_K\_DDT\times\text{DENSK}\times\text{VKL}
\text{CFoetus}\_K\_DDT=4.7

\text{AB}\_DDT'=\text{QB}\times(\text{CBlood}\_DDT-\text{CVB}\_DDT)
\text{CVB}\_DDT=\text{CB}\_DDT/\text{PB}\_DDT
\text{CB}\_DDT=\text{AB}\_DDT/\text{VBL}
\text{CBB}\_DDT=\text{CB}\_DDT/(\text{DENSB}\times\text{FATPERCB})
\text{init}\ \text{AB}\_DDT=\text{CFoetus}\_B\_DDT\times\text{DENSB}\times\text{VBL}
\text{CFoetus}\_B\_DDT=3.9

S11
ABlood_DDT'=QF*CVF_DDT+QR*CVR_DDT+QL*CVL_DDT+QK*CVK_DDT+QB*CVB_DDT-
(QF+QR+QL+QK+QB)*CBlood_DDT
CBlood_DDT=ABlood_DDT/VBloodL
CBloodG_DDT=CBlood_DDT/(DENSBlood*FATPERCBlood)
init ABlood_DDT=CfoetusBlood_DDT*DENSBlood*VBloodL
CfoetusBlood_DDT=0.000001

ABioaccumulation_DDT'=Dose_DDT-HepMet_DDT
init ABioaccumulation_DDT=CfoetusF_DDT*DENSF*VFL+CfoetusR_DDT*DENSR*VRL+
CfoetusL_DDT*DENS*VLL+CfoetusK_DDT*DENS*VKL+CfoetusB_DDT*DENS*VBL+CfoetusBlood_DDT*

\{------------------------MASS BALANCE------------------------\}

TOTAL_DDT=ABioaccumulation_DDT
CALCULATION_DDT=AF_DDT+AR_DDT+AL_DDT+AB_DDT+AK_DDT+ABlood_DDT
MASSBALANCE_DDT=(TOTAL_DDT-CALCULATION_DDT)/(TOTAL_DDT+1E-30)*100

\{------------------------MASS-BALANCE EQUATIONS DDD------------------------\}

AF_DDD'=QF*(CBlood_DDD-CVF_DDD)
CVF_DDD=AF_DDD/PF_DDD
CF_DDD=AF_DDD/VFL
CFG_DDD=CF_DDD/(DENSF*FATPERCF)
init AF_DDD=CfoetusF_DDD*DENSF*VFL
CfoetusF_DDD=2943.8

AR_DDD'=QR*(CBlood_DDD-CVR_DDD)
CVR_DDD=CR_DDD/PR_DDD
CR_DDD=AR_DDD/VRL
CRG_DDD=CR_DDD/(DENSR*FATPERCR)
init AR_DDD=CfoetusR_DDD*DENSR*VRL
CfoetusR_DDD=0.000001

AL_DDD'=(QL*(CBlood_DDD-CVL_DDD)-HepMet_DDD+DOSE_DDD+PercDDT*HepMet_DDT)
CVL_DDD=CL_DDD/PL_DDD
CL_DDD=AL_DDD/VLL
CLG_DDD=CL_DDD/(DENS*FATPERCL)
init AL_DDD=CfoetusL_DDD*DENS*VLL
CfoetusL_DDD=37.6

PercDDT=0.502
\{UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS\}

CLint_DDD=0.111919
\{Biotransformation in liver; calculated according Verner et al. (2009) using an elimination half life of 3.6 years; UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS\}
Eh_DDD=(CLint_DDD*VLL)/(CLint_DDD*VLL+QL)
HepMet_DDD=QL*Eh_DDD*CBlood_DDD

AK_DDD'=QK*(CBlood_DDD-CVK_DDD)
CVK_DDD=CK_DDD/PK_DDD
CK_DDD=AK_DDD/VKL
CKG_DDD=CK_DDD/(DENS*FATPERCK)
init AK_DDD=CfoetusK_DDD*DENS*VKL
CfoetusK_DDD=35.5
\[ AB\_DDD = QB \times (CB\_Blood\_DDD - CVB\_DDD) \]
\[ CVB\_DDD = CB\_DDD / PB\_DDD \]
\[ CB\_DDD = AB\_DDD / VBL \]
\[ CBG\_DDD = AB\_DDD / (DENSB*FATPERCB) \]
\[ init\ AB\_DDD = CFoetusB\_DDD \times DENSB \times VBL \]
\[ CFoetusB\_DDD = 27.6 \]

\[ AB\_Blood\_DDD = QF \times CVF\_DDD + QR \times CVR\_DDD + QL \times CVL\_DDD + QK \times CVK\_DDD + QB \times CVB\_DDD \]
\[ init\ AB\_Blood\_DDD = CFoetusBlood\_DDD \times DENSB \times VB\_Blood \]
\[ CFoetusBlood\_DDD = 0.000001 \]

\[ AB\_Bioaccumulation\_DDD = Dose\_DDD - HepMet\_DDD + PercDDT \times HepMet\_DDD \]
\[ init\ AB\_Bioaccumulation\_DDD = CFoetusF\_DDD \times DENSF \times VFL + CFoetusR\_DDD \times DENSR \times VRL + CFoetusL\_DDD \times DENSL \times VLL + CFoetusK\_DDD \times DENSK \times VKL + CFoetusB\_DDD \times DENSB \times VBL + CFoetusBlood\_DDD \times DENSBlood \times VB\_Blood \]

\[ \text{TOTAL\_DDD} = AB\_Bioaccumulation\_DDD \]
\[ \text{CALCULATION\_DDD} = AF\_DDD + AR\_DDD + AL\_DDD + AB\_DDD + AK\_DDD + AB\_Blood\_DDD \]
\[ \text{MASSBALANCE\_DDD} = (\text{TOTAL\_DDD} - \text{CALCULATION\_DDD}) / (\text{TOTAL\_DDD} + 1.0) \times 100 \]

\[ AF\_DDD = QF \times (CB\_Blood\_DDD - CVF\_DDD) \]
\[ CVF\_DDD = CF\_DDD / PF\_DDD \]
\[ CF\_DDD = AF\_DDD / VFL \]
\[ CFG\_DDD = CF\_DDD / (DENSF*FATPERCF) \]
\[ init\ AF\_DDD = CFoetusF\_DDD \times DENSF \times VFL \]
\[ CFoetusF\_DDD = 3351.6 \]

\[ AR\_DDD = QR \times (CB\_Blood\_DDD - CVR\_DDD) \]
\[ CVR\_DDD = CR\_DDD / PR\_DDD \]
\[ CR\_DDD = AR\_DDD / VRL \]
\[ CRG\_DDD = CR\_DDD / (DENSR*FATPERCR) \]
\[ init\ AR\_DDD = CFoetusR\_DDD \times DENSR \times VRL \]
\[ CFoetusR\_DDD = 0.000001 \]

\[ AL\_DDD = QL \times (CB\_Blood\_DDD - CVL\_DDD) - HepMet\_DDD + DOSE\_DDD + ((1.0 - PercDDT) \times HepMet\_DDD) + (PercDDT \times HepMet\_DDD) \]
\[ CVL\_DDD = CL\_DDD / PL\_DDD \]
\[ CL\_DDD = AL\_DDD / VLL \]
\[ CLG\_DDD = CL\_DDD / (DENSL*FATPERCL) \]
\[ init\ AL\_DDD = CFoetusL\_DDD \times DENSL \times VLL \]
\[ CFoetusL\_DDD = 50.5 \]

\[ PercDDT = 0.10 \]

\[ CLint\_DDD = 0.036037 \]

\[ \text{Biotransformation in liver; calculated according Verner et al. (2009) using an elimination half life of 11.8 years;} \]

\[ Eu\_DDD = (CLint\_DDD \times VLL) / (CLint\_DDD \times VLL + QL) \]

\[ HepMet\_DDD = QL \times Eu\_DDD \times CB\_Blood\_DDD \]

\[ \text{UPDATED WITH BAYESIAN APPROACH AND MCMC SIMULATIONS} \]
\[ \text{AK\_DDE}' = QK \times (\text{CBlood\_DDE} - \text{CVK\_DDE}) \]
\[ \text{CVK\_DDE} = \frac{\text{CK\_DDE}}{PK\_DDE} \]
\[ \text{CK\_DDE} = \frac{\text{AK\_DDE}}{VKL} \]
\[ \text{CKG\_DDE} = \frac{\text{CK\_DDE}}{(\text{DENSK}\times\text{FATPERCK})} \]
\[ \text{init \ AK\_DDE} = CFoetusK\_DDE \times \text{DENSK} \times VKL \]
\[ \text{CFoetusK\_DDE} = 43.3 \]

\[ \text{AB\_DDE}' = QB \times (\text{CBlood\_DDE} - \text{CVB\_DDE}) \]
\[ \text{CVB\_DDE} = \frac{\text{CB\_DDE}}{PB\_DDE} \]
\[ \text{CB\_DDE} = \frac{\text{AB\_DDE}}{VBL} \]
\[ \text{CBG\_DDE} = \frac{\text{CB\_DDE}}{(\text{DENSB}\times\text{FATPERCB})} \]
\[ \text{init \ AB\_DDE} = CFoetusB\_DDE \times \text{DENSB} \times VBL \]
\[ \text{CFoetusB\_DDE} = 42.0 \]

\[ \text{AB\_Blood\_DDE}' = QF \times \text{CVF\_DDE} + QR \times \text{CVR\_DDE} + QL \times \text{CVL\_DDE} + QK \times \text{CVK\_DDE} + QB \times \text{CVB\_DDE} - (QF + QR + QL + QK + QB) \times \text{CBlood\_DDE} \]
\[ \text{CBlood\_DDE} = \frac{\text{AB\_Blood\_DDE}}{VBloodL} \]
\[ \text{CBloodG\_DDE} = \frac{\text{CBlood\_DDE}}{(\text{DENSBlood}\times\text{FATPERCBlood})} \]
\[ \text{init \ AB\_Blood\_DDE} = CFoetusBlood\_DDE \times \text{DENSBlood} \times VBloodL \]
\[ \text{CFoetusBlood\_DDE} = 0.000001 \]

\[ \text{AB\_Bioaccumulation\_DDE}' = \text{Dose\_DDE} - \text{HepMet\_DDE} + ((1.0 - \text{PercDDT}) \times \text{HepMet\_DDT}) + (\text{PercDDD}\times\text{HepMet\_DDD}) \]
\[ \text{init \ AB\_Bioaccumulation\_DDE} = CFoetusF\_DDE \times \text{DENSF} \times VFL + CFoetusR\_DDE \times \text{DENSR} \times VRL + CFoetusL\_DDE \times \text{DENSL} \times VLL + CFoetusK\_DDE \times \text{DENSK} \times VKL + CFoetusB\_DDE \times \text{DENSB} \times VBL + CFoetusBlood\_DDE \times \text{DENSBlood} \times VBloodL \]

\{------------------------MASS BALANCE------------------------\}

\[ \text{TOTAL\_DDE} = \text{AB\_Bioaccumulation\_DDE} \]
\[ \text{CALCULATION\_DDE} = AF\_DDE + AR\_DDE + AL\_DDE + AB\_DDE + AK\_DDE + AB\text{\_Blood\_DDE} \]
\[ \text{MASSBALANCE\_DDE} = (\text{TOTAL\_DDE} - \text{CALCULATION\_DDE}) / (\text{TOTAL\_DDE} + \text{1E-30}) \times 100 \]
List of references:


