Supplementary Materials

Probabilistic risk assessment of gold nanoparticles after intravenous administration by integrating \textit{in vitro} and \textit{in vivo} toxicity with physiologically based pharmacokinetic modeling

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**Figure S1.** Schematic showing human AuNP-PBPK model following IV administration.

This model structure was adapted from our earlier PBPK model for AuNPs in mice, rats, pigs, and humans (Lin et al., 2016a).
Figure S2. Comparison among fitted dose-response relationships describing concentration-dependent cell death fraction in hepatocytes exposed to 40 nm AuNP-BPEI-HP using (A) exponential, (B) Weibull, (C) Logistic, and (D) Hill model, respectively. AuNP, gold nanoparticle; BPEI, branched polyethylenimine; HP, human plasma proteins.
Figure S3. PBPK model-predicted internal organ concentrations of AuNPs. A, B, and C represent low, medium, and high scaled human doses (LHD, MHD, and HHD), respectively. D-O represent maximum internal concentrations in liver (pink) (D, H, L), venous plasma (purple) (E, I, M), kidney (blue) (F, J, N), and skin (orange) (G, K, O) estimated from human AuNP-PBPK model within 24 h after intravenous injection with LHD, MHD, and HHD, respectively.
Figure S4. Exceedance risk profiles of internal concentration-associated cell death fraction in hepatocytes (A–C), HUVEC (D–I), HRPTEC (J–L), keratinocytes (M–O), and PMNs (P–R) given low (dotted line), medium (dashed line), high (solid line) scaled intravenous doses.
### Table S1. Summary of selected *in vitro* studies used for dose-response analyses.

<table>
<thead>
<tr>
<th>Human cell type</th>
<th>Size and surface coating of AuNPs</th>
<th>Cell density and incubated medium</th>
<th>Exposed AuNP concentration (μg/ml)</th>
<th>Incubated duration</th>
<th>Detection reagent/method/instrument</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinocytes</td>
<td>40, 80 nm; BPEI, LA, PEG coated w/ HP or HSA</td>
<td>10⁴/96-well KGM-Gold&lt;sup&gt;TM&lt;/sup&gt;</td>
<td>12.5–100</td>
<td>24, 48 h</td>
<td>AlamarBlue/fluorescence microplate reader</td>
<td>Li and Monteiro-Riviere (2016)</td>
</tr>
<tr>
<td>Hepatocytes</td>
<td>40, 80 nm; BPEI, LA, PEG coated w/ HP or HSA</td>
<td>6×10⁴/96-well Williams’ medium E</td>
<td>0–400</td>
<td>24 h</td>
<td>AlamarBlue/fluorescence microplate reader</td>
<td>Choi et al. (2017)</td>
</tr>
<tr>
<td>HUVEC</td>
<td>40, 80 nm; BPEI, LA, PEG coated w/ HP or HSA</td>
<td>10⁴/96-well EGM-2</td>
<td>0–100</td>
<td>24 h</td>
<td>AlamarBlue/fluorescence microplate reader</td>
<td>Chandran et al. (2017)</td>
</tr>
<tr>
<td>HRPTEC</td>
<td>40, 80 nm; BPEI, LA, PEG coated w/ HP or HSA</td>
<td>1.25×10⁴/96-well EpiCM</td>
<td>0–200</td>
<td>24 h</td>
<td>AlamarBlue/fluorescence microplate reader</td>
<td>Ortega et al. (2017)</td>
</tr>
<tr>
<td>PMNs</td>
<td>20, 70 nm; NA</td>
<td>10⁷/96-well RPMI-1640</td>
<td>0–100</td>
<td>24 h</td>
<td>Hema 3/cytology light microscopy</td>
<td>Noël et al. (2016)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BPEI, branched polyethylenimine; LA, lipoic acid; PEG, polyethylene glycol; HP, human plasma proteins; HSA, human serum albumin; HRPTEC, human renal proximal tubule epithelial cells; HUVEC, human umbilical vein endothelial cells; PMN, polymorphonuclear neutrophil cells; NA, not available.
Table S2. Parameters used in *in vitro* sedimentation, diffusion and dosimetry (ISDD) model and estimated deposited fractions of AuNPs.

<table>
<thead>
<tr>
<th>Size/surface coating of AuNPs</th>
<th>Hydrodynamic diameter in the DI water (nm) (^a)</th>
<th>Hydrodynamic diameter in the medium at 37ºC (nm) (^a)</th>
<th>Density of AuNPs (g/mL) (^a)</th>
<th>Fractal dimension (DF) (^b)</th>
<th>Packing factor (PF) (^b)</th>
<th>Viscosity of medium at 37ºC (N s/m(^2)) (^b)</th>
<th>Density of medium (g/mL) (^a)</th>
<th>Medium height (cm) (^a)</th>
<th>Deposited fraction of AuNPs at 6, 12, and 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 nm; BPEI</td>
<td>59.4 ± 0.2</td>
<td>177.7 ± 3.3</td>
<td>19.32</td>
<td>2.3</td>
<td>0.637</td>
<td>0.00069</td>
<td>1</td>
<td>0.3125</td>
<td>0.41/0.79/1</td>
</tr>
<tr>
<td>80 nm; BPEI</td>
<td>118.9 ± 0.8</td>
<td>150.3 ± 1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91/1/1</td>
</tr>
<tr>
<td>40 nm; LA</td>
<td>48.7 ± 0.3</td>
<td>63.9 ± 0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30/0.52/0.83</td>
</tr>
<tr>
<td>80 nm; LA</td>
<td>103.8 ± 4.0</td>
<td>123.2 ± 0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83/1/1</td>
</tr>
<tr>
<td>40 nm; PEG</td>
<td>71.1 ± 0.2</td>
<td>64.1 ± 0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30/0.52/0.83</td>
</tr>
<tr>
<td>80 nm; PEG</td>
<td>133.1 ± 0.8</td>
<td>126.7 ± 0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84/1/1</td>
</tr>
</tbody>
</table>

\(^a\) Reported as average values of hydrodynamic diameter (mean ± SD) that were adopted from Choi et al. (2017).

\(^b\) Defaulted values adopted from Hinderliter et al. (2010).
Table S3. Summary of intravenously (IV) administered dosages of AuNPs applied in animal studies and associated scaled dosages that were implemented in human PBPK modeling.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Size/coating/modification of AuNPs</th>
<th>IV dosage (mg/kg)</th>
<th>Dosing level</th>
<th>Detection method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult rats</td>
<td>1.4, 2.8, 5, 18, 80, 200 nm; TPPMS, TGA, CA</td>
<td>0.005–0.3</td>
<td>Animal</td>
<td>Low</td>
<td>NAA</td>
</tr>
<tr>
<td>Adult mice</td>
<td>50, 80, 100, 150 nm; PEG</td>
<td>0.5–0.6</td>
<td>Human</td>
<td>0.001–0.05</td>
<td>Medium</td>
</tr>
<tr>
<td>Adult mice</td>
<td>Nanorod: 65 nm; PEG</td>
<td>1.2–2.7</td>
<td>0.1–0.2</td>
<td>Medium</td>
<td>ICP-MS</td>
</tr>
<tr>
<td>Adult mice</td>
<td>2, 40 nm; citrate</td>
<td>0.6–3.2</td>
<td>0.05–0.3</td>
<td>Medium</td>
<td>AMG</td>
</tr>
<tr>
<td>Adult rats</td>
<td>10, 50, 100, 250 nm; NA</td>
<td>0.3–0.4</td>
<td>0.06–0.08</td>
<td>Medium</td>
<td>ICP-MS</td>
</tr>
<tr>
<td>Adult mice</td>
<td>13 nm; PEG</td>
<td>0.2–4.3</td>
<td>0.01–0.3</td>
<td>Medium</td>
<td>ICP-MS</td>
</tr>
<tr>
<td>Adult rats</td>
<td>18.4 nm; citrate</td>
<td>0.6–1.0</td>
<td>0.1–0.2</td>
<td>Medium</td>
<td>GF-AAS</td>
</tr>
<tr>
<td>Adult mice/rats</td>
<td>Nanorod: 60 nm; PEG</td>
<td>0.1</td>
<td>0.01–0.02</td>
<td>Medium</td>
<td>AAS</td>
</tr>
<tr>
<td>Adult mice</td>
<td>110 nm; PEG</td>
<td>10.3 ± 1.3</td>
<td>0.8 ± 0.1</td>
<td>High</td>
<td>NAA</td>
</tr>
<tr>
<td>Adult mice</td>
<td>2 – 20 nm; GSH, pMBA</td>
<td>36.9–86.4</td>
<td>2.9–6.9</td>
<td>High</td>
<td>ICP-MS</td>
</tr>
</tbody>
</table>

Human dosages were scaled from animal IV dosages based on conversion factors adopted from Nair and Jacob (2016).

Administered dosing levels were classified based on Khlebtsov and Dykman (2011).

Abbreviations: AAS, atomic absorption spectrometry; AMG, autometallography; CA, cysteamine (2-aminoethanethiol); GF-AAS, graphite furnace atomic absorption spectrometry; GSH, glutathione; ICP-MS, inductively coupled plasma mass spectrometry; NA, not available; NAA, neutron activation analysis; PEG, polyethylene glycol; pMBA, p-mercaptobenzoic acid; TGA, thioglycolic acid (mercaptoacetic acid); TPPMS, triphenylphosphine m-monosulfonate.
<table>
<thead>
<tr>
<th>Size/surface coating of AuNPs</th>
<th>Model</th>
<th>$E_{\text{min}}$</th>
<th>$E_{\text{max}}$</th>
<th>$EC_{50}$</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\gamma$ or $n$</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 nm; BPEI</td>
<td>Exponential</td>
<td>0.0001 ± 0.06</td>
<td>1</td>
<td>261.86</td>
<td>0.003 ± 0.001*</td>
<td></td>
<td></td>
<td>0.7781***</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>0.04 ± 0.03</td>
<td>1</td>
<td>184.51</td>
<td>0.005 ± 0.0002***</td>
<td>5.53 ± 1.76*</td>
<td></td>
<td>0.9396***</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>0.03 ± 0.03</td>
<td>1</td>
<td>183.97</td>
<td>7.64 ± 2.31**</td>
<td>0.04 ± 0.01**</td>
<td></td>
<td>0.9391***</td>
</tr>
<tr>
<td></td>
<td>Hill</td>
<td>0.03 ± 0.02</td>
<td>1</td>
<td>185.01 ± 7.89***</td>
<td></td>
<td></td>
<td></td>
<td>6.16 ± 1.86**</td>
</tr>
<tr>
<td>80 nm; BPEI</td>
<td>Exponential</td>
<td>0.00001 ± 0.05</td>
<td>1</td>
<td>231.67</td>
<td>0.003 ± 0.001***</td>
<td></td>
<td></td>
<td>0.8401***</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>0.002 ± 0.04</td>
<td>1</td>
<td>213.19</td>
<td>0.004 ± 0.0004***</td>
<td>1.59 ± 0.34***</td>
<td></td>
<td>0.8908***</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>0.05 ± 0.04</td>
<td>1</td>
<td>191.98</td>
<td>5.88 ± 1.69**</td>
<td>0.03 ± 0.009**</td>
<td></td>
<td>0.8869***</td>
</tr>
<tr>
<td></td>
<td>Hill</td>
<td>0.02 ± 0.04</td>
<td>1</td>
<td>210.07 ± 15.52***</td>
<td></td>
<td></td>
<td></td>
<td>2.46 ± 0.57***</td>
</tr>
<tr>
<td>40 nm; BPEI-HP</td>
<td>Exponential</td>
<td>0.0001 ± 0.08</td>
<td>1</td>
<td>261.86</td>
<td>0.003 ± 0.001*</td>
<td></td>
<td></td>
<td>0.6359**</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>0.0001 ± 0.04</td>
<td>1</td>
<td>255.73</td>
<td>0.003 ± 0.0003***</td>
<td>2.11 ± 0.50***</td>
<td></td>
<td>0.8916***</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>0.00001 ± 0.09</td>
<td>1</td>
<td>228.73</td>
<td>4.41 ± 2.75**</td>
<td>0.02 ± 0.01</td>
<td></td>
<td>0.7774**</td>
</tr>
<tr>
<td></td>
<td>Hill</td>
<td>0.00001 ± 0.03</td>
<td>1</td>
<td>273.30 ± 23.36***</td>
<td></td>
<td></td>
<td></td>
<td>2.47 ± 0.45***</td>
</tr>
<tr>
<td>80 nm; BPEI-HP</td>
<td>Exponential</td>
<td>0.00001 ± 0.03</td>
<td>1</td>
<td>1059.87</td>
<td>0.001 ± 0.0003*</td>
<td></td>
<td></td>
<td>0.5616***</td>
</tr>
<tr>
<td></td>
<td>Weibull</td>
<td>0.007 ± 0.004</td>
<td>1</td>
<td>394.52</td>
<td>0.002 ± 0.00003***</td>
<td>3.70 ± 0.27***</td>
<td></td>
<td>0.9887***</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>0.001 ± 0.006</td>
<td>1</td>
<td>394.97</td>
<td>5.61 ± 0.42***</td>
<td>0.01 ± 0.001***</td>
<td></td>
<td>0.9882***</td>
</tr>
<tr>
<td></td>
<td>Hill</td>
<td>0.007 ± 0.004</td>
<td>1</td>
<td>394.66 ± 5.45***</td>
<td></td>
<td></td>
<td></td>
<td>4.22 ± 0.28***</td>
</tr>
</tbody>
</table>

*p < 0.05; ** p < 0.01; *** p < 0.001.

$^a$ Parameter values of $EC_{50}$ for exponential, Weibull, and Logistic models were estimated using TableCurve 2D based on constructed dose-response models.

Abbreviations: $E_{\text{min}}$ and $E_{\text{max}}$, minimum and maximum fraction of cell death; $EC_{50}$, exposure concentration leading to half maximum fractional cell death (μg/ml); $\alpha$, location parameter for the Logistic model; $\beta$, slope parameter in dose-response models; $\gamma$, exponent parameter for the Weibull model; $n$, Hill coefficient or exponent; $r^2$, coefficient of determination.
Table S5. **EC$_{5}$** and **EC$_{10}$** with mean and 95% CI estimates based on the built dose-response relationships.

<table>
<thead>
<tr>
<th>Human cell types</th>
<th>Size/surface coating of AuNPs</th>
<th><strong>EC$_{5}$</strong> (µg/ml)</th>
<th><strong>EC$_{10}$</strong> (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocytes</td>
<td>40 nm; BPEI-HP</td>
<td>82.8 (40.2–125.3)</td>
<td>112.0 (81.7–152.8)</td>
</tr>
<tr>
<td></td>
<td>80 nm; BPEI-HP</td>
<td>189.2 (173.4–208.1)</td>
<td>230.3 (215.2–246.6)</td>
</tr>
<tr>
<td></td>
<td>40 nm; BPEI</td>
<td>95.4 (46.5–144.3)</td>
<td>121.1 (89.7–152.4)</td>
</tr>
<tr>
<td></td>
<td>80 nm; BPEI</td>
<td>49.0 (9.5–88.5)</td>
<td>77.3 (30.9–108.8)</td>
</tr>
<tr>
<td>HUVEC</td>
<td>40 nm; BPEI</td>
<td>43.7 (37.3–50.2)</td>
<td>51.0 (45.5–55.8)</td>
</tr>
<tr>
<td></td>
<td>80 nm; BPEI</td>
<td>42.3 (33.4–51.2)</td>
<td>49.9 (40.4–56.7)</td>
</tr>
<tr>
<td></td>
<td>40 nm; PEG</td>
<td>33.8 (12.0–55.6)</td>
<td>62.2 (31.4–101.2)</td>
</tr>
<tr>
<td>HRPTEC</td>
<td>40 nm; BPEI</td>
<td>18.5 (11.0–26.1)</td>
<td>25.8 (14.2–32.0)</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>40 nm; BPEI</td>
<td>29.7 (23.2–36.2)</td>
<td>38.2 (33.3–43.4)</td>
</tr>
<tr>
<td></td>
<td>80 nm; BPEI</td>
<td>NA</td>
<td>12.8 (0–28.8)</td>
</tr>
</tbody>
</table>

**Abbreviations:** **EC$_{5}$** and **EC$_{10}$**, exposed concentrations leading to 5% and 10% maximum fractional cell death, respectively; BPEI, branched polyethylenimine; PEG, polyethylene glycol; HP, human plasma proteins; HUVEC, human umbilical vein endothelial cells; HRPTEC, human renal proximal tubule epithelial cells; NA, not available.
Human PBPK model code for AuNPs

{ [AuNP-PBPK model for humans extrapolated from rats with the main model code adopted from Lin et al. (2016a) and incorporated with Monte Carlo simulation for Lognormally distributed intravenous (IV) dosages to estimate distribution profiles of internal AuNP exposure concentration] }

METHOD RK4

STARTTIME = 0
STOPTIME = 24
DT = 0.00125
DTOUT = 0.005

; Blood flow rate (Fraction of cardiac output, unitless)
QCC = 16.5 ; Cardiac output (L/h/kg\(^{0.75}\)) (Brown et al., 1997)
QLC = 0.227 ; Fraction of blood flow to liver (Brown et al., 1997)
QBRC = 0.114 ; Fraction of blood flow to brain (Brown et al., 1997)
QKC = 0.175 ; Fraction of blood flow to kidneys (Brown et al., 1997)
QSC = 0.01375 ; Fraction of blood flow to spleen (Davies and Morris, 1993)

; Tissue volumes (Fraction of body weight, unitless)
BW = 70 ; Body weight (kg) (Brown et al., 1997)
VLC = 0.0257 ; Liver (Brown et al., 1997)
VBR = 0.02 ; Brain (Brown et al., 1997)
VKC = 0.0044 ; Kidneys (Brown et al., 1997)
VSC = 0.00257 ; Spleen (Davies and Morris, 1993)
VLuC = 0.008 ; Lungs (Brown et al., 1997)
VPlasmaC = 0.079 ; Plasma (Davies and Morris, 1993; Brown et al., 1997)

; Blood volume fraction in organs and tissues (percentage of organs/tissues, unitless)
BVL = 0.11 ; Liver (Brown et al., 1997)
BVBR = 0.04 ; Brain (Brown et al., 1997)
BVK = 0.36 ; Kidneys (Brown et al., 1997)
BVS = 0.3 ; Spleen (Brown et al., 1997, average of mouse, rat, and dog)
BVlu = 0.3867 ; Lungs (Brown et al., 1997, average of mouse, rat, and dog)
Brest = 0.01 ; Rest of body (Brown et al., 1997, assume equal to the muscle)

; Tissue:plasma distribution coefficients (P, unitless); these values were from our published mouse PBPK model for gold nanoparticles (Lin et al., 2016b)
PL = 0.08 ; Liver
PBR = 0.15 ; Brain
PK = 0.15 ; Kidneys
PS = 0.15 ; Spleen
PLu = 0.15 ; Lungs
Prest = 0.15 ; Rest of body

; Membrane-limited permeability coefficient constants (PA, unitless); these values were from our published mouse PBPK model for gold nanoparticles (Lin et al., 2016b)
PALC = 0.001 ; Liver
PABRC = 0.000001 ; Brain
PAKC = 0.001 ; Kidneys
PASC = 0.001 ; Spleen
PALuC = 0.001 ; Lungs
PArestC = 0.000001 ; Rest of body
Endocytic parameters; RES represent phagocytic cells; L, S, K, Lu, rest represent liver, spleen, kidneys, lungs, and rest of body, respectively.

KLRESrelease = 0.025; Release rate constant of phagocytic cells (h⁻¹)
KLRESmax = 20; Maximum uptake rate constant of phagocytic cells (h⁻¹)
KLRES50 = 24; Time reaching half maximum uptake rate (h)
KLRESn = 0.5; Hill coefficient (unitless)
ALRESScap = 195; Uptake capacity per tissue weight (μg/g tissue)

KLRESrelease = 0.09; Release rate constant of phagocytic cells (h⁻¹)
KSRESmax = 10; Maximum uptake rate constant of phagocytic cells (h⁻¹)
KSRES50 = 24; Time reaching half maximum uptake rate (h)
KSRESn = 0.5; Hill coefficient (unitless)
ASREScap = 150; Uptake capacity per tissue weight (μg/g tissue)

KLRESrelease = 0.0075; Release rate constant of phagocytic cells (h⁻¹)
KKRESmax = 0.5; Maximum uptake rate constant of phagocytic cells (h⁻¹)
KKRES50 = 24; Time reaching half maximum uptake rate (h)
KKRESn = 0.5; Hill coefficient (unitless)
AKREScap = 330; Uptake capacity per tissue weight (μg/g tissue)

KLuresrelease = 0.07; Release rate constant of phagocytic cells (h⁻¹)
KLuRESmax = 1; Maximum uptake rate constant of phagocytic cells (h⁻¹)
KLuRES50 = 24; Time reaching half maximum uptake rate (h)
KLuRESn = 0.5; Hill coefficient (unitless)
ALLuREScap = 150; Uptake capacity per tissue weight (μg/g tissue)

KRestRESlease = 0.1; Release rate constant of phagocytic cells (h⁻¹)
KrestRESmax = 80; Maximum uptake rate constant of phagocytic cells (h⁻¹)
KrestRES50 = 24; Time reaching half maximum uptake rate (h)
KrestRESn = 0.5; Hill coefficient (unitless)
ArestREScap = 1.5; Uptake capacity per tissue weight (μg/g tissue)

Biliary excretion:
KbileC = 0.0008; Biliary clearance (L/hr/kg⁰.⁷⁵)
L/hr/kg changed to L/h/kg⁰.⁷⁵ for interspecies extrapolation

Urine excretion:
KurineC = 0.0008; Urine clearance (L/hr/kg⁰.⁷⁵)
L/hr changed to L/h/kg⁰.⁷⁵ for interspecies extrapolation

IV dosing:
Timeiv = 0.005; IV infusion time (h), set, approximately 15-20 seconds, on average 18 sec
PDOSeiv = 0.001286; mg/kg

Low IV dose (<0.1 mg/kg in animal dose):
LDM = 0.0817; low animal dose (mean) (mg/kg)
LDSD = 0.0699; low animal dose (SD) (mg/kg)
LDLOGM = LOGN(LDM²/(LDM²+LDSD²)⁰.⁵); logarithmized animal dose (mean) (mg/kg)
LDLOGSD = (LOGN(1+LDSD²/LDM²))⁰.⁵; logarithmized animal dose (SD) (mg/kg)
LPDOSeiv = EXP(NORMAL(LDLOGM, LDLOGSD)); lognormally distributed animal dose

Medium IV dose (0.1-10 mg/kg in animal dose):
MDM = 0.87; medium animal dose (mean) (mg/kg)
MDSD = 0.16; medium animal dose (SD) (mg/kg)
MDLOGM = LOGN(MDM²/(MDM²+MDSD²)⁰.⁵); logarithmized animal dose (mean) (mg/kg)
MDLOGSD = (LOGN(1+MDSD^2/MDM^2))^0.5; logarithmized animal dose (SD) (mg/kg)
MPDOSEiv = EXP(NORMAL(MDLOGM, MDLOGSD)); lognormally distributed animal dose

; High IV dose (>10 mg/kg in animal dose)
HDM = 33.81; high animal dose (mean) (mg/kg)
HDSD = 5.33; high animal dose (SD) (mg/kg)
HDLOGM = LOGN(HDM^2/(HDM^2+HDSD^2)^0.5); logarithmized animal dose (mean) (mg/kg)
HDLOGSD = (LOGN(1+HDSD^2/HDM^2))^0.5; logarithmized animal dose (SD) (mg/kg)
HPDOSEiv = EXP(NORMAL(HDLOGM, HDLOGSD)); lognormally distributed animal dose

; Scaled parameters
; Cardiac output and regional blood flow (L/h)
QC = QCC*BW^0.75; Cardiac output
QL = QC*QLC; Blood flow to liver
QBR = QC*QBRC; Blood flow to brain
QK = QC*QKC; Blood flow to kidneys
QS = QC*QSC; Blood flow to spleen
Qrest = QC-QL-QBR-QK-QS; Blood flow to rest of body
Qbal = QC-QL-QBR-QK-QS-Qrest; Blood flow balance equation

; Tissue volumes (L)
VL = BW*VLC; Liver
VBR = BW*VBR; Brain
VK = BW*VKC; Kidneys
VS = BW*VSC; Spleen
VLu = BW*VLu; Lungs
VPlasma = BW*VPlasma; Plasma
Vrest = BW-VL-VBR-VK-VS-VLu-VPlasma; Rest of body
Vbal = BW-VL-VBR-VK-VS-VLu-VPlasma-Vrest; Tissue volume balance equation

; Capillary blood and tissue interstitium volume in each tissue (L)
VLb = VL*BVL; Weight/volume of capillary blood in liver compartment
VLt = VL-VLb; Weight/volume of tissue in liver compartment
VBRb = VBR*BVBR; Weight/volume of capillary blood in brain compartment
VBRt = VBR-VBRb; Weight/volume of tissue in brain compartment
VKb = VK*VKb; Weight/volume of capillary blood in kidney compartment
VKt = VK-VKb; Weight/volume of tissue in kidney compartment
VSb = VS*BVS; Weight/volume of capillary blood in spleen compartment
VSt = VS-VSb; Weight/volume of tissue in spleen compartment
VLub = VLu*BVLu; Weight/volume of capillary blood in lung compartment
VLut = VLu-VLub; Weight/volume of tissue in lung compartment
Vrestb = Vrest*BVrest; Weight/volume of capillary blood in rest of body compartment
Vrestt = Vrest-Vrestb; Weight/volume of tissue in rest of body compartment

; Permeability coefficient-surface area cross-product (L/h)
PAL = PALC*QL; Liver
PABR = PABRC*QBR; Brain
PAK = PAKC*QK; Kidneys
PAS = PASC*QS; Spleen
PALu = PALuC*QC; Lungs
PArest = PArestC*Qrest; Rest of body

; Endocytosis rate (h⁻¹)
KLRESUP = (KLRESmax*TIME*KLRESn)/(KLRES50*KLRESn+TIME*KLRESn)*(1-(ALRES/(ALREScap*VL))); Liver
KSRESUP = (KSRESmax*TIME^KSRESn)/
(KSRES50^KRESn+TIME^KSRESn)*(1-(ASRES/(ASREScap*VS))) ; Spleen
KKRESUP = (KKRESmax*TIME^KKRESn)/
(KKRES50^KKRESn+TIME^KKRESn)*(1-(AKRES/(AKREScap*VK))) ; Kidneys
KLuRESUP = (KLuRESmax*TIME^KLuRESn)/
(KLuRES50^KLuRESn+TIME^KLuRESn)*(1-(ALuRES/(ALuREScap*VLu))) ; Lungs
KrestRESUP = (KrestRESmax*TIME^KrestRESn)/
(KrestRES50^KrestRESn+TIME^KrestRESn)*(1-(ArestRES/(ArestREScap*Vrest))) ; Rest of body

; IV Dosing scenarios
DOSEiv = PDoseiv*BW ; dose amount (mg)
IVR = DOSEiv/Timeiv ; dosing rate (mg/h)
RIV = IVR*(1.-step(1,Timeiv)) ; scenario of dosing rate (mg/h)
d/dt(AIV) = RIV
init AIV = 0

LDOSEiv = LPDOSEiv*BW ; low amount of dose (mg)
LIVR = LDOSEiv/Timeiv ; low dosing rate (mg/h)
LRIV = LIVR*(1.-step(1,Timeiv)) ; scenario of low dosing rate (mg/h)
d/dt(AIVL) = LRIV
init AIVL = 0

MDOSEiv = MPDOSEiv*BW ; medium amount of dose (mg)
MIVR = MDOSEiv/Timeiv ; medium dosing rate (mg/h)
MRIV = MIVR*(1.-step(1,Timeiv)) ; scenario of medium dosing rate (mg/h)
d/dt(AIVM) = MRIV
init AIVM = 0

HDOSEiv = HPDOSEiv*BW ; high amount of dose (mg)
HIVR = HDOSEiv/Timeiv ; high dosing rate (mg/h)
HRIV = HIVR*(1.-step(1,Timeiv)) ; scenario of high dosing rate (mg/h)
d/dt(AIVH) = HRIV
init AIVH = 0

; Elimination
Kbile = KbileC*BW^0.75 ; allometric biliary excretion rate (L/h)
Kurine = KurineC*BW^0.75 ; allometric urinary excretion rate (L/h)

{Blood compartment}
; CA = Arterial blood concentration (mg/L or μg/mL)
RA = QC*CVLu - QC*CA
d/dt(AA) = RA
init AA = 0
CA = AA/(VPlasma*0.2)

; CV = Venous blood concentration (mg/L or μg/mL)
RV = QL*CVL + QBR*CVBR + QK*CVK + Qrest*CVrest + LRIV - QC*CV
d/dt(AV) = RV
init AV = 0
CV = AV/(VPlasma*0.8)

APlasma = AA+AV
CPlasma = APlasma/VPlasma
\[ RL_{ub} = QC \times (CV - CV_{Lu}) - PALu \times CV_{Lu}/PLu + RLuRES_{release} - KLuRESup \times ALub \]
\[ \frac{d}{dt}(ALub) = RLub \]
\[ init \ ALub = 0 \]
\[ CV_{Lu} = ALub/VLub \]
\[ RL_{ut} = PALu \times CV_{Lu} - (PALu \times CLut)/PLu \]
\[ \frac{d}{dt}(ALut) = RLut \]
\[ init \ ALut = 0 \]
\[ CLut = ALut/VLut \]
\[ ALutan = ALub + ALut \]
\[ CLu = ALutan/VLu \]
\[ RLuRES = KLuRESup \times ALub - KLuRES_{release} \times ALuRES \]
\[ RLuRES_{up} = KLuRESup \times ALub \]
\[ RLuRES_{release} = KLuRES_{release} \times ALuRES \]
\[ \frac{d}{dt}(ALuRES) = RLuRES \]
\[ init \ ALuRES = 0 \]
\[ CLung = (ALutan + ALuRES)/VLu \]
\[ CLungtissue = (ALutan + ALuRES)/VLut \]
\[ ALungtissue = ALutan + ALuRES \]

\[ (Brain \ compartment) \]

\[ RB_{rb} = QB_{rb} \times (CA - CVBR) - PABR \times CVBR + (PABR \times CBR_{t})/PBR \]
\[ \frac{d}{dt}(ABRb) = RB_{rb} \]
\[ init \ ABRb = 0 \]
\[ CVBR = ABRb/VBRb \]
\[ RB_{rt} = PABR \times CVBR - (PABR \times CBR_{t})/PBR \]
\[ \frac{d}{dt}(ABRt) = RB_{rt} \]
\[ init \ ABRt = 0 \]
\[ CBR_{t} = ABRt/VBRt \]
\[ ABR_{total} = ABRb + ABRt \]
\[ CBR = ABR_{total}/VBR \]

\[ (Rest \ of \ body \ compartment) \]

\[ R_{restb} = Q_{rest} \times (CA - CVrest) - PArest \times CVrest + (PArest \times Crest_{t})/Prest + R_{restRES}_{release} - KrestRESup \times Arestb \]
\[ \frac{d}{dt}(Arestb) = R_{restb} \]
\[ init \ Arestb = 0 \]
\[ CVrest = Arestb/Vrestb \]
\[ R_{restt} = PArest \times CVrest - (PArest \times Crest_{t})/Prest \]
\[ \frac{d}{dt}(Arestt) = R_{restt} \]
\[ init \ Arestt = 0 \]
\[ Crest = Arestt/Vrestt \]
\[ Arest_{total} = Arestb + Arestt \]
\[ Crest = Arest_{total}/Vrest \]
\[ R_{restRES} = KrestRESup \times Arestb - KrestRES_{release} \times ArestRES \]
\[ R_{restRES}_{up} = KrestRESup \times Arestb \]
R_{restRESrelease} = K_{restRESrelease} \cdot A_{restRES}
\frac{d}{dt}(A_{restRES}) = R_{restRES}
init A_{restRES} = 0

C_{restall} = (A_{resttotal}+A_{restRES})/V_{rest}
C_{resttissue} = (A_{restt}+A_{restRES})/V_{restt}
A_{resttissue} = A_{restt}+A_{restRES}

{Kidney compartment}
; Membrane-limited model
R_{Kb} = Q_K \cdot (C_A - C_{VK}) - P_{AK} \cdot C_{VK} + (P_{AK} \cdot C_{Kt})/P_K - R_{urine} + R_{KRESrelease} - K_{KRESUP} \cdot A_{Kb}
\frac{d}{dt}(A_{Kb}) = R_{Kb}
init A_{Kb} = 0
C_{VK} = A_{Kb}/V_{Kb}
R_{Kt} = P_{AK} \cdot C_{VK} - (P_{AK} \cdot C_{Kt})/P_K
\frac{d}{dt}(A_{Kt}) = R_{Kt}
init A_{Kt} = 0
C_{Kt} = A_{Kt}/V_{Kt}
A_{Ktotal} = A_{Kb}+A_{Kt}
C_{K} = A_{Ktotal}/V_K
R_{KRES} = K_{KRESUP} \cdot A_{Kb} - K_{KRESrelease} \cdot A_{KRES}
R_{KRESUP} = K_{KRESUP} \cdot A_{Kb}
R_{KRESrelease} = K_{KRESrelease} \cdot A_{KRES}
\frac{d}{dt}(A_{KRES}) = R_{KRES}
init A_{KRES} = 0
C_{Kidney} = (A_{Ktotal}+A_{KRES})/V_K
C_{Kidneytissue} = (A_{Kt}+A_{KRES})/V_{Kt}
A_{Kidneytissue} = A_{Kt}+A_{KRES}

; Urinary excretion
R_{urine} = K_{urine} \cdot C_{VK} \text{ mg/h}
\frac{d}{dt}(A_{urine}) = R_{urine}
init A_{urine} = 0

{Spleen compartment}
; Membrane-limited model
R_{Sb} = Q_S \cdot (C_A - C_{VS}) - P_{AS} \cdot C_{VS} + (P_{AS} \cdot C_{St})/P_S + R_{SRESrelease} - K_{SRESUP} \cdot A_{Sb}
\frac{d}{dt}(A_{Sb}) = R_{Sb}
init A_{Sb} = 0
C_{VS} = A_{Sb}/V_{Sb}
R_{St} = P_{AS} \cdot C_{VS} - (P_{AS} \cdot C_{St})/P_S
\frac{d}{dt}(A_{St}) = R_{St}
init A_{St} = 0
C_{St} = A_{St}/V_{St}
A_{Stotal} = A_{Sb}+A_{St}
C_{S} = A_{Stotal}/V_S
R_{SRES} = K_{SRESUP} \cdot A_{Sb} - K_{SRESrelease} \cdot A_{SRES}
R_{SRESUP} = K_{SRESUP} \cdot A_{Sb}
R_{SRESrelease} = K_{SRESrelease} \cdot A_{SRES}
\[
\frac{d}{dt}(\text{ASRES}) = \text{RSRES} \\
\text{init ASRES} = 0 \\
\]

\[
\text{CSpleen} = (\text{AStotal+ASRES})/\text{VS} \\
\text{Cspleentissue} = (\text{ASt+ASRES})/\text{VSt} \\
\text{ASpleentissue} = \text{ASt+ASRES} \\
\]

\{Liver compartment\} \\
: Membrane-limited model \\
\[
\text{RLb} = QL*(CA-\text{CVL}) + QS*CVS - \text{PAL}\cdot\text{CVL} + (\text{PAL}\cdot\text{CLt})/\text{PL} - \text{Rbile} + \text{RLRESrelease} - \text{KLRESUP}\cdot\text{ALb} \\
\frac{d}{dt}(\text{ALb}) = \text{RLb} \\
\text{init ALb} = 0 \\
\text{CVL} = \text{ALb}/\text{VLb} \\
\]

\[
\text{RLt} = \text{PAL}\cdot\text{CVL} - (\text{PAL}\cdot\text{CLt})/\text{PL} \\
\frac{d}{dt}(\text{ALT}) = \text{RLt} \\
\text{init ALT} = 0 \\
\text{CLt} = \text{ALT}/\text{VLt} \\
\text{ALtotal} = \text{ALb}+\text{ALT} \\
\text{CL} = \text{ALtotal}/\text{VL} \\
\]

\[
\text{RLRES} = \text{KLRESUP}\cdot\text{ALb}-\text{KLRESrelease}\cdot\text{ALRES} \\
\text{RLRESUP} = \text{KLRESUP}\cdot\text{ALb} \\
\text{RLRESrelease} = \text{KLRESrelease}\cdot\text{ALRES} \\
\frac{d}{dt}(\text{ALRES}) = \text{RLRES} \\
\text{init ALRES} = 0 \\
\]

\[
\text{CLiver} = (\text{ALtotal}+\text{ALRES})/\text{VL} \\
\text{CLivertissue} = (\text{ALT}+\text{ALRES})/\text{VLt} \\
\text{ALivertissue} = \text{ALT}+\text{ALRES} \\
\]

: Biliary excretion \\
\[
\text{Rbile} = \text{Kbile}\cdot\text{CVL} ; \text{mg/h} \\
\frac{d}{dt}(\text{Abile}) = \text{Rbile} \\
\text{init Abile} = 0 \\
\]

\{Mass balance\} \\
\[
\text{Tmass} = \text{AA}+\text{AV}+\text{ALtotal}+\text{ABRtotal}+\text{AKtotal}+\text{ALutotal}+\text{Aresttotal}+\text{AStotal}+\text{Abile}+\text{Aurine}+\text{ALRES}+\text{ASRES}+\text{ALuRES}+\text{AKRES}+\text{ArestRES} \\
\text{Bal} = \text{AILVL}-\text{Tmass} \\
\]
Reference


El-Sayed MA, Shabaka AA, El-Shabrawy OA, Yassin NA, Mahmoud SS, El-Shenawy SM,


