Supplementary materials

Physiologically based pharmacokinetic modeling of nanoceria systemic distribution in rats suggests dose- and route-dependent biokinetics

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Link to supplementary information: https://ki.box.com/s/exiu59ri25lihwzhk08fy5gxa93b1tmq

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Abbreviations

AUC	area under the curve
BW	body weight
CeO_2	cerium dioxide
CL_f	clearance rate constant to feces
CL_u	clearance rate constant to urine
fBl_{tissue}	fraction of tissue volume that is blood
fQ_{tissue}	fraction of cardiac output to tissue
$fRBl_{brain}$	residual fraction of brain blood after harvesting
$fRBl_{tissue}$	residual fraction of tissue blood after harvesting
fW_{tissue}	tissue weight, fraction of body weight
it	intratracheally
iv	intravenously
k_{ab0}	uptake rate constant to phagocytic cells
k_{sab0}	uptake rate constant to phagocytic cells in spleen
M_{cap}	maximum uptake capacity per phagocytic cell
$n_{cap\ in\ tissue}$	number of phagocytizing cells per gram tissue
P	partition coefficient between blood and tissue
PBPK	physiologically based pharmacokinetic
R^2	coefficient of determination
X_{brain}	permeability coefficient from blood to brain.
X_{fast}	permeability coefficient from blood to liver, spleen, and bone marrow
X_{rest}	permeability coefficient from blood to lung, kidney, heart, and carcass

Nanoparticle-independent physiologically based pharmacokincetic (PBPK) model parameters

Table S1. Summary of nanoparticle-independent PBPK model parameters.[a]

Parameter (unit)	Description	Blood	Bone Marrow	Brain	Heart	Kidney	Liver	Lung	Other	Spleen
fQ_{tissue} (unitless)	Fraction of cardiac output to tissue	-	0.0267	0.02	0.051	0.141	0.183	1	$1-\Sigma fQ_{tissue}$	0.0146
fW_{tissue} (unitless) [b]	Tissue weight, fraction of body weight	0.074	0.03	0.006	0.003	0.007	0.034	0.005	$1-\Sigma fW_{tissue}$	0.002
fBl_{tissue} (unitless) [b]	Fraction of tissue volume that is blood	0.2 Arterial 0.8 Venous	0.1	0.03	0.26	0.16	0.21	0.36	0.04	0.22
$fRBl_{tissue}$ (unitless) [c]	Residual fraction of tissue blood after harvesting	-	0.177	0.346	0.177	0.177	0.177	0.177	0.177	0.177

[a] Parameter values from Li *et al.*[1]

Sensitivity analysis

Table S2. Relative sensitivity coefficient for 5 nm at 10 h (85 mg/kg)

AUC 10 h	Blood	Bone marrow	Brain	Feces	Heart	Kidney	Liver	Lung	Other tissues	PC	Spleen	Urine
Body weight	1.13	1.02	1.07	0.06	1.11	1.11	1.02	1.06	0.86	0.96	1.07	0.09
Dose rate	1.90	0.38	1.85	1.47	1.82	1.80	0.45	0.93	1.66	0.71	1.44	1.65
Exposure duration	1.88	0.33	1.82	1.32	1.79	1.78	0.40	0.91	1.58	0.64	1.36	1.57
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.12	0.04	-0.13	-0.20	-0.12	-0.12	0.15	-0.05	-0.15	0.05	-0.14	-0.16
k_{sab0}	-0.07	-0.01	-0.06	-0.03	-0.06	-0.06	-0.01	-0.03	-0.05	0.02	0.76	-0.05
k_{de}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
M_{cap}	-0.89	0.62	-0.84	-0.47	-0.81	-0.79	0.54	0.07	-0.66	0.29	-0.44	-0.64
$n_{cap\ in\ blood}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.31	0.72	-0.30	-0.18	-0.30	-0.29	-0.06	-0.15	-0.24	0.10	-0.21	-0.24
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.56	-0.09	-0.52	-0.28	-0.52	-0.52	0.60	-0.27	-0.40	0.18	-0.34	-0.39
$n_{cap\ in\ lung}$	-0.01	0.00	-0.01	-0.01	-0.01	-0.01	0.00	0.50	-0.01	0.00	-0.01	-0.01
$n_{cap\ in\ other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ spleen}$	-0.01	0.00	-0.01	0.00	-0.01	-0.01	0.00	-0.01	-0.01	0.00	0.12	-0.01
P	-0.28	0.13	-0.29	0.61	0.55	0.59	0.18	0.28	-0.33	0.00	0.55	-0.34
X_{brain}	0.00	0.00	0.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.00	0.01	-0.01
X_{rest}	-0.51	-0.08	-0.47	-0.22	-0.43	-0.44	-0.09	-0.24	0.58	0.15	-0.30	-0.34
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fQ_{bone\ marrow}$	0.02	0.02	0.02	0.00	0.02	0.02	0.00	0.01	-0.04	-0.01	0.01	0.01
fQ_{brain}	0.02	0.00	0.23	0.01	0.02	0.02	0.00	0.01	-0.02	-0.01	0.01	0.01
fQ_{heart}	0.05	0.01	0.04	0.02	0.08	0.04	0.01	0.02	-0.05	-0.01	0.03	0.03
fQ_{kidney}	0.13	0.02	0.12	0.05	0.12	0.15	0.02	0.06	-0.15	-0.04	0.07	0.08
fQ_{spleen}	0.01	0.00	0.01	0.01	0.01	0.01	0.00	0.01	-0.02	0.00	0.03	0.01
fQ_{liver}	0.16	0.03	0.15	0.09	0.15	0.15	0.03	0.08	-0.20	-0.05	0.09	0.11
$fRBl_{brain}$	0.00	0.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.01	0.00	0.00	0.10	0.07	0.01	0.07	0.05	0.00	0.00	0.00
fW_{blood}	0.80	-0.07	-0.22	-0.38	-0.21	-0.21	-0.10	-0.11	-0.31	-0.15	-0.27	-0.31
$fW_{bone\ marrow}$	-0.36	0.91	-0.35	-0.27	-0.35	-0.34	-0.08	-0.18	-0.32	0.08	-0.27	-0.31
fW_{brain}	0.00	0.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	0.96	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	-0.01	0.00	-0.01	-0.01	-0.01	0.96	0.00	0.00	-0.01	0.00	-0.01	-0.01
fW_{liver}	-0.70	-0.13	-0.67	-0.51	-0.66	-0.66	0.84	-0.34	-0.58	0.19	-0.50	-0.58
fW_{lung}	-0.02	0.00	-0.02	-0.02	-0.02	-0.02	0.00	0.98	-0.02	0.00	-0.01	-0.02
fW_{spleen}	-0.08	-0.01	-0.08	-0.04	-0.08	-0.08	-0.02	-0.04	-0.06	0.02	0.93	-0.06

Table S3. Relative sensitivity coefficient for 5 nm at 30 days (end of exposure, 85 mg/kg)

AUC 30 days	Blood	Bone marrow	Brain	Feces	Heart	Kidney	Liver	Lung	Other tissues	PC	Spleen	Urine
Body weight	1.21	1.02	0.97	0.21	1.09	1.07	1.03	1.01	0.96	1.00	1.16	0.21
Dose rate	1.58	0.06	1.78	1.80	0.69	0.57	0.10	0.05	1.78	0.99	1.31	1.78
Exposure duration	1.58	0.06	1.78	1.80	0.69	0.57	0.10	0.05	1.78	0.99	1.31	1.78
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.12	0.08	-0.09	-0.09	-0.05	-0.04	0.10	0.02	-0.08	0.00	-0.08	-0.09
k_{sab0}	-0.05	0.00	-0.07	-0.07	-0.02	-0.02	0.00	0.00	-0.07	0.00	0.71	-0.07
k_{de}	0.19	-0.10	0.15	0.15	0.08	0.07	-0.16	-0.02	0.14	0.00	-0.24	0.15
M_{cap}	-0.58	0.94	-0.77	-0.79	0.32	0.43	0.90	0.95	-0.78	0.00	-0.32	-0.78
$n_{cap\ in\ blood}$	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.20	0.90	-0.25	-0.26	-0.09	-0.07	0.01	0.00	-0.26	0.00	-0.18	-0.26
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.57	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.64	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.37	0.04	-0.49	-0.50	-0.16	-0.13	0.89	0.01	-0.49	0.00	-0.34	-0.49
$n_{cap\ in\ lung}$	-0.01	0.00	-0.01	-0.01	0.00	0.00	0.00	0.94	-0.01	0.00	-0.01	-0.01
$n_{cap\ in\ other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ spleen}$	-0.02	0.00	-0.02	-0.02	-0.01	-0.01	0.00	0.00	-0.02	0.00	0.21	-0.02
P	-0.17	0.09	-0.17	0.83	0.31	0.27	0.11	0.04	-0.15	0.00	0.62	-0.17
X_{brain}	0.00	0.00	0.96	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
X_{rest}	-0.80	-0.09	-0.81	-0.82	-0.35	-0.29	-0.11	-0.05	0.16	0.01	-0.63	-0.81
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fQ_{bone\ marrow}$	0.04	0.00	0.04	0.04	0.02	0.01	0.01	0.00	-0.01	0.00	0.03	0.04
fQ_{brain}	0.03	0.00	0.99	0.03	0.01	0.01	0.00	0.00	-0.01	0.00	0.02	0.03
fQ_{heart}	0.07	0.01	0.07	0.07	0.03	0.03	0.01	0.00	-0.01	0.00	0.06	0.07
fQ_{kidney}	0.20	0.02	0.21	0.21	0.09	0.07	0.03	0.01	-0.04	0.00	0.16	0.21
fQ_{spleen}	0.02	0.00	0.02	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.03	0.02
fQ_{liver}	0.26	0.03	0.27	0.27	0.11	0.10	0.04	0.02	-0.05	0.00	0.21	0.27
$fRBl_{brain}$	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.00	0.00	0.00	0.05	0.02	0.00	0.00	0.00	0.00	0.00	0.00
fW_{blood}	1.00	0.00	-0.01	-0.01	0.00	0.00	0.00	0.00	-0.01	0.00	0.00	-0.01
$fW_{bone\ marrow}$	-0.23	1.01	-0.28	-0.28	-0.10	-0.08	0.00	0.00	-0.28	0.00	-0.20	-0.28
fW_{brain}	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{liver}	-0.44	0.02	-0.55	-0.57	-0.19	-0.16	1.01	0.00	-0.55	0.00	-0.39	-0.55
fW_{lung}	-0.01	0.00	-0.01	-0.01	0.00	0.00	0.00	1.00	-0.01	0.00	-0.01	-0.01
fW_{spleen}	-0.07	0.00	-0.09	-0.09	-0.03	-0.03	0.00	0.00	-0.09	0.00	0.93	-0.09

Table S4. Relative sensitivity coefficient for 5 nm at 10 h (11 mg/kg)

AUC 10 h	Blood	Bone marrow	Brain	Feces	Heart	Kidney	Liver	Lung	Other tissues	PC	Spleen	Urine
Body weight	1.06	0.99	1.00	0.04	1.03	1.02	1.04	1.01	0.82	1.00	1.05	0.05
Dose rate	1.10	0.99	1.10	1.08	0.72	0.63	1.01	0.54	1.09	0.99	1.09	1.09
Exposure duration	1.10	0.93	1.09	0.97	0.71	0.63	0.95	0.49	1.04	0.93	1.03	1.03
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.73	0.07	-0.71	-0.64	-0.46	-0.41	0.24	0.05	-0.65	0.08	-0.65	-0.66
k_{sab0}	-0.02	-0.02	-0.02	-0.02	-0.02	-0.01	-0.02	-0.01	-0.02	0.00	0.91	-0.02
k_{de}	0.01	0.00	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
M_{cap}	-0.10	0.01	-0.10	-0.08	0.28	0.37	-0.01	0.45	-0.09	0.01	-0.08	-0.09
$n_{cap\ in\ blood}$	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.04	0.07	-0.04	-0.03	-0.02	-0.02	-0.03	-0.01	-0.03	0.00	-0.03	-0.03
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.43	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.05	-0.04	-0.04	-0.04	-0.03	-0.03	0.04	-0.02	-0.04	0.00	-0.04	-0.04
$n_{cap\ in\ lung}$	-0.02	-0.02	-0.02	-0.02	-0.01	-0.01	-0.02	0.49	-0.02	0.00	-0.02	-0.02
$n_{cap\ in\ other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
P	-0.75	0.04	-0.74	0.29	0.05	0.06	0.22	0.06	-0.70	0.05	0.25	-0.70
X_{brain}	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	-0.06	0.08	-0.06	-0.03	-0.04	-0.04	-0.03	-0.03	-0.06	0.00	-0.04	-0.06
X_{rest}	-0.13	-0.11	-0.13	-0.11	-0.04	-0.03	-0.11	0.03	0.82	0.01	-0.12	-0.12
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	0.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fQ_{bone\ marrow}$	-0.07	0.16	-0.07	-0.07	-0.05	-0.04	-0.06	-0.03	-0.11	0.01	-0.07	-0.07
fQ_{brain}	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.00	-0.03	0.00	0.00	0.00
fQ_{heart}	0.01	0.01	0.01	0.01	0.05	0.01	0.01	0.01	-0.08	0.00	0.01	0.01
fQ_{kidney}	0.03	0.03	0.03	0.03	0.02	0.06	0.03	0.01	-0.21	0.00	0.03	0.03
fQ_{liver}	0.02	0.02	0.02	0.06	0.01	0.01	0.06	0.01	-0.29	0.00	0.02	0.02
fQ_{spleen}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.02	0.00	0.03	0.00
$fRBl_{brain}$	0.00	0.00	0.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.00	0.00	0.00	0.07	0.04	0.00	0.01	0.05	0.00	0.00	0.00
fW_{blood}	1.00	-0.07	-0.02	-0.14	-0.01	-0.01	-0.07	-0.05	-0.08	-0.07	-0.07	-0.07
$fW_{bone\ marrow}$	-0.29	0.54	-0.28	-0.24	-0.18	-0.16	-0.24	-0.13	-0.26	0.02	-0.26	-0.26
fW_{brain}	0.00	0.00	0.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	0.95	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	0.00	0.00	0.00	-0.01	0.00	0.95	0.00	0.00	-0.01	0.00	0.00	0.00
fW_{liver}	-0.51	-0.43	-0.50	-0.49	-0.33	-0.29	0.52	-0.23	-0.48	0.04	-0.47	-0.47
fW_{lung}	-0.03	-0.03	-0.03	-0.03	-0.02	-0.02	-0.03	0.90	-0.03	0.00	-0.03	-0.03
fW_{spleen}	-0.02	-0.02	-0.02	-0.02	-0.02	-0.01	-0.02	-0.01	-0.02	0.00	0.95	-0.02

Table S5. Relative sensitivity coefficient for 5 nm at 30 days (end of exposure, 11 mg/kg)

		Bone							Other			
AUC 720 h	Blood	marrow	Brain	Feces	Heart	Kidney	Liver	Lung	tissues	PC	Spleen	Urine
Body weight	1.05	1.02	0.83	0.05	1.00	1.00	1.05	1.02	0.82	1.00	1.06	0.06
Dose rate	0.90	0.97	1.13	1.14	0.06	0.06	1.01	0.40	1.14	1.00	1.13	1.14
Exposure duration	0.90	0.96	1.12	1.14	0.06	0.06	1.01	0.40	1.14	1.00	1.13	1.14
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.55	0.10	-0.71	-0.75	-0.02	-0.01	0.22	0.08	-0.70	0.00	-0.71	-0.72
k_{sab0}	-0.02	-0.02	-0.02	-0.02	0.00	0.00	-0.02	-0.01	-0.02	0.00	0.94	-0.02
k_{de}	0.33	-0.03	0.28	0.29	0.01	0.01	-0.07	-0.09	0.28	0.00	-0.06	0.28
M_{cap}	0.10	0.03	-0.12	-0.14	0.94	0.94	-0.01	0.60	-0.14	0.00	-0.13	-0.14
$n_{cap\ in\ blood}$	0.22	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.05	0.10	-0.05	-0.05	0.00	0.00	-0.05	-0.02	-0.05	0.00	-0.06	-0.05
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.94	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.95	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.05	-0.05	-0.06	-0.06	0.00	0.00	0.06	-0.02	-0.06	0.00	-0.06	-0.06
$n_{cap\ in\ lung}$	-0.02	-0.02	-0.02	-0.02	0.00	0.00	-0.02	0.64	-0.02	0.00	-0.02	-0.02
$n_{cap\ in\ other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
P	-0.57	0.08	-0.73	0.22	0.01	0.01	0.20	0.07	-0.73	0.00	0.23	-0.74
X_{brain}	0.00	0.00	0.94	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	-0.02	0.05	-0.04	-0.02	0.00	0.00	-0.02	-0.01	-0.04	0.00	-0.03	-0.04
X_{rest}	-0.17	-0.16	-0.18	-0.18	-0.01	-0.01	-0.17	-0.05	0.80	0.00	-0.19	-0.18
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fQ_{bone\ marrow}$	-0.02	0.10	-0.04	-0.04	0.00	0.00	-0.03	-0.01	-0.09	0.00	-0.04	-0.04
fQ_{brain}	0.01	0.01	0.95	0.01	0.00	0.00	0.01	0.00	-0.03	0.00	0.01	0.01
fQ_{heart}	0.02	0.02	0.02	0.02	0.00	0.00	0.02	0.01	-0.07	0.00	0.02	0.02
fQ_{kidney}	0.04	0.04	0.05	0.05	0.00	0.00	0.04	0.02	-0.20	0.00	0.05	0.05
fQ_{liver}	0.05	0.04	0.05	0.07	0.00	0.00	0.07	0.02	-0.27	0.00	0.05	0.05
fQ_{spleen}	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.00	-0.02	0.00	0.02	0.00
$fRBl_{brain}$	0.00	0.00	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{blood}	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fW_{bone\ marrow}$	-0.26	0.59	-0.31	-0.32	-0.02	-0.02	-0.28	-0.12	-0.32	0.00	-0.32	-0.32
fW_{brain}	0.00	0.00	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{liver}	-0.38	-0.42	-0.50	-0.53	-0.03	-0.02	0.53	-0.17	-0.50	0.00	-0.49	-0.50
fW_{lung}	-0.02	-0.03	-0.03	-0.03	0.00	0.00	-0.03	0.97	-0.03	0.00	-0.03	-0.03
fW_{spleen}	-0.02	-0.02	-0.02	-0.02	0.00	0.00	-0.02	-0.01	-0.02	0.00	0.96	-0.02

Table S6. Relative sensitivity coefficients for 30 nm at 10 h (87 mg/kg)

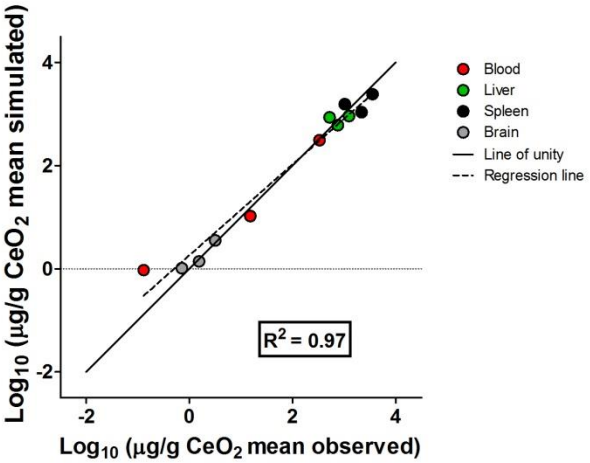
AUC 10 h	Blood	Bone marrow	Brain	Feces	Heart	Kidney	Liver	Lung	Other tissues	PC	Spleen	Urine
Body weight	1.03	1.01	1.03	0.01	1.00	1.00	1.01	1.01	0.86	0.97	1.01	0.02
Dose rate	1.24	0.61	1.24	1.07	1.18	1.16	0.80	0.61	1.18	0.73	0.81	1.14
Exposure duration	1.21	0.55	1.21	0.91	1.14	1.12	0.73	0.57	1.11	0.66	0.74	1.05
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.25	0.29	-0.25	-0.17	-0.23	-0.23	0.43	-0.08	-0.21	0.28	-0.14	-0.21
k_{sab0}	-0.07	-0.03	-0.07	-0.04	-0.07	-0.07	-0.04	-0.03	-0.06	0.08	0.65	-0.06
k_{de}	0.01	0.00	0.00	0.00	0.00	0.00	-0.01	0.00	0.00	-0.01	-0.01	0.00
M_{cap}	-0.24	0.38	-0.24	-0.07	-0.17	-0.15	0.20	0.39	-0.18	0.26	0.18	-0.14
$n_{cap\ in\ blood}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.10	0.42	-0.10	-0.03	-0.09	-0.09	-0.04	-0.05	-0.08	0.11	-0.04	-0.06
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.10	-0.03	-0.10	-0.03	-0.09	-0.08	0.26	-0.05	-0.07	0.11	-0.04	-0.06
$n_{cap\ in\ lung}$	-0.01	0.00	-0.01	0.00	-0.01	-0.01	0.00	0.49	-0.01	0.01	0.00	-0.01
$n_{cap\ in\ other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ spleen}$	-0.03	-0.01	-0.03	-0.01	-0.03	-0.03	-0.01	-0.01	-0.02	0.04	0.27	-0.02
P	-0.37	0.34	-0.37	0.73	0.17	0.27	0.44	0.11	-0.33	0.31	0.48	-0.32
X_{brain}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{rest}	-0.10	-0.04	-0.10	-0.04	0.00	-0.01	-0.05	-0.03	0.57	0.10	-0.05	-0.07
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.19	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.35	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
fQ_{spleen}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.02	0.00	0.01	0.00
fQ_{liver}	0.03	0.01	0.03	0.02	0.03	0.03	0.02	0.01	-0.19	-0.03	0.01	0.02
fQ_{brain}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.02	0.00	0.00	0.00
fQ_{heart}	0.01	0.00	0.01	0.00	0.09	0.01	0.00	0.00	-0.05	-0.01	0.00	0.01
fQ_{kidney}	0.02	0.01	0.02	0.01	0.02	0.10	0.01	0.01	-0.14	-0.03	0.01	0.02
$fQ_{bone\ marrow}$	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-0.03	0.00	0.00	0.00
$fRBl_{brain}$	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.02	0.00	0.00	0.35	0.25	0.04	0.19	0.35	0.00	0.01	0.00
fW_{blood}	0.48	-0.33	-0.52	-0.68	-0.52	-0.51	-0.43	-0.27	-0.61	-0.41	-0.45	-0.61
$fW_{bone\ marrow}$	-0.20	0.91	-0.20	-0.12	-0.18	-0.18	-0.11	-0.09	-0.18	0.18	-0.11	-0.15
fW_{brain}	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	0.91	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	0.00	0.00	0.00	0.00	0.00	0.91	0.00	0.00	-0.01	0.00	0.00	0.00
fW_{lung}	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	0.97	-0.01	0.01	-0.01	-0.01
fW_{liver}	-0.29	-0.12	-0.29	-0.16	-0.27	-0.26	0.84	-0.14	-0.26	0.28	-0.15	-0.22
fW_{spleen}	-0.11	-0.04	-0.11	-0.05	-0.10	-0.09	-0.05	-0.05	-0.09	0.11	0.94	-0.07

Table S7. Relative sensitivity coefficients for 30 nm at 90 d (end of experiment, 87 mg/kg)

AUC 90 days	Blood	Bone marrow	Brain	Feces	Heart	Kidney	Lung	Liver	Other tissues	PC	Spleen	Urine
Body weight	1.19	1.07	1.13	0.18	1.08	1.06	1.03	1.09	0.94	1.00	1.10	0.18
Dose rate	1.27	0.23	1.32	1.49	0.53	0.41	0.10	0.35	1.47	0.99	0.40	1.49
Exposure duration	1.27	0.23	1.32	1.49	0.53	0.41	0.10	0.35	1.47	0.99	0.40	1.49
CL_f	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CL_u	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
k_{ab0}	-0.20	0.27	-0.20	-0.20	-0.08	-0.06	0.09	0.35	-0.16	0.01	-0.09	-0.20
k_{sab0}	-0.05	-0.01	-0.05	-0.06	-0.02	-0.02	0.00	-0.01	-0.06	0.00	0.46	-0.06
k_{de}	0.27	-0.29	0.27	0.28	0.11	0.09	-0.08	-0.38	0.24	-0.01	-0.41	0.28
M_{cap}	-0.27	0.76	-0.32	-0.48	0.47	0.59	0.90	0.64	-0.47	0.01	0.59	-0.48
$n_{cap\ in\ blood}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ bone\ marrow}$	-0.09	0.68	-0.11	-0.15	-0.04	-0.03	0.01	0.02	-0.15	0.00	0.02	-0.15
$n_{cap\ in\ brain}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ heart}$	0.00	0.00	0.00	0.00	0.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ kidney}$	0.00	0.00	0.00	0.00	0.00	0.67	0.00	0.00	0.00	0.00	0.00	0.00
$n_{cap\ in\ liver}$	-0.12	0.06	-0.15	-0.23	-0.05	-0.04	0.02	0.61	-0.23	0.00	0.05	-0.23
$n_{cap\ in\ lung}$	-0.01	0.00	-0.01	-0.01	0.00	0.00	0.86	0.00	-0.01	0.00	0.00	-0.01
$n_{cap\ in\ other\ tissues}$	-0.01	-0.01	-0.01	0.00	0.00	0.00	0.00	-0.01	0.00	0.00	-0.01	0.00
$n_{cap\ in\ spleen}$	-0.05	0.03	-0.06	-0.09	-0.02	-0.01	0.01	0.02	-0.09	0.00	0.54	-0.09
P	-0.26	0.27	-0.26	0.72	0.17	0.16	0.10	0.34	-0.23	0.00	0.37	-0.27
X_{brain}	0.00	0.00	0.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{fast}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
X_{rest}	-0.72	-0.28	-0.71	-0.69	-0.30	-0.23	-0.12	-0.36	0.26	0.01	-0.38	-0.69
$fBlood_{art}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{bone\ marrow}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{brain}$	0.00	0.00	0.77	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{heart}$	0.00	0.00	0.00	0.00	0.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{kidney}$	0.00	0.00	0.00	0.00	0.00	0.08	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{liver}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{lung}$	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00
$fblood_{other\ tissues}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fblood_{spleen}$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fQ_{spleen}	0.02	0.01	0.02	0.02	0.01	0.01	0.00	0.01	-0.01	0.00	0.01	0.02
fQ_{liver}	0.24	0.09	0.23	0.23	0.10	0.08	0.04	0.12	-0.08	0.00	0.12	0.23
fQ_{brain}	0.03	0.01	0.25	0.03	0.01	0.01	0.00	0.01	-0.01	0.00	0.01	0.02
fQ_{heart}	0.07	0.03	0.06	0.06	0.03	0.02	0.01	0.03	-0.02	0.00	0.03	0.06
fQ_{kidney}	0.18	0.07	0.18	0.17	0.08	0.06	0.03	0.09	-0.06	0.00	0.10	0.17
$fQ_{bone\ marrow}$	0.03	0.01	0.03	0.03	0.01	0.01	0.01	0.02	-0.01	0.00	0.02	0.03
$fRBl_{brain}$	0.00	0.00	0.77	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$fRBl_{tissue}$	0.00	0.00	0.00	0.00	0.14	0.08	0.01	0.00	0.00	0.00	0.00	0.00
fW_{blood}	0.99	0.01	-0.01	-0.03	0.00	0.00	0.01	0.02	-0.03	-0.01	0.01	-0.03
$fW_{bone\ marrow}$	-0.14	1.01	-0.16	-0.21	-0.06	-0.05	0.00	0.00	-0.21	0.00	-0.01	-0.21
fW_{brain}	0.00	0.00	0.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{heart}	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{kidney}	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
fW_{lung}	-0.01	0.00	-0.01	-0.01	0.00	0.00	1.00	0.00	-0.01	0.00	0.00	-0.01
fW_{liver}	-0.23	0.04	-0.26	-0.36	-0.10	-0.07	0.02	1.02	-0.36	0.00	0.01	-0.36
fW_{spleen}	-0.10	0.02	-0.11	-0.15	-0.04	-0.03	0.01	0.01	-0.15	0.00	1.01	-0.15

Calibration 5 nm

A



B

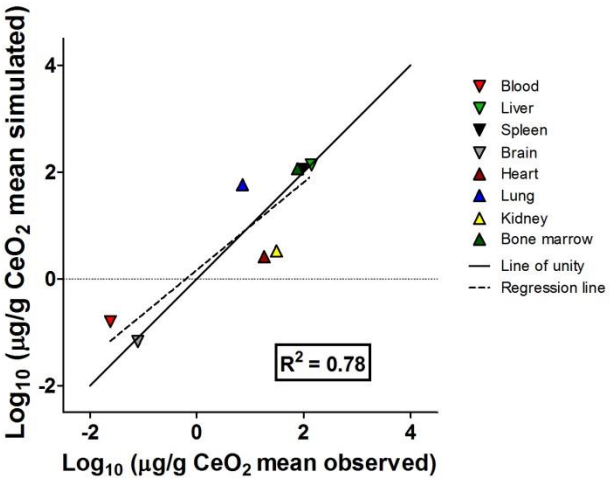


Figure S1. Observed versus simulated concentrations in tissues.

PBPK model calibration of 5 nm ceria. (A) Compares logs of simulated and observed mean concentration in different tissues of rats at various time-points, following 1 h *iv* infusion of 85 mg/kg body weight.[2] (B) Comparison of logs of simulated and observed mean concentration in different tissues of rats, 30 days after 1 h *iv* infusion of 11 mg/kg body weight. [3]

Comparison of the 5 nm calibrated PBPK model to independent data set with 3 nm nanoceria

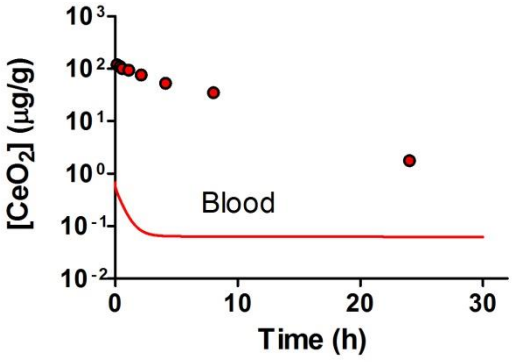


Figure S2. Observed versus simulated concentrations in blood.

Comparison of the 5 nm calibrated PBPK model against independent data set with 3-nm ceria. Simulated (solid curve) and observed (symbols) time courses of the nanoceria concentration in blood following an *iv* bolus dose of 10 mg/kg body weight.[4]

Comparison of the 30 nm calibrated PBPK model to independent data sets with nanoceria around 30 nm

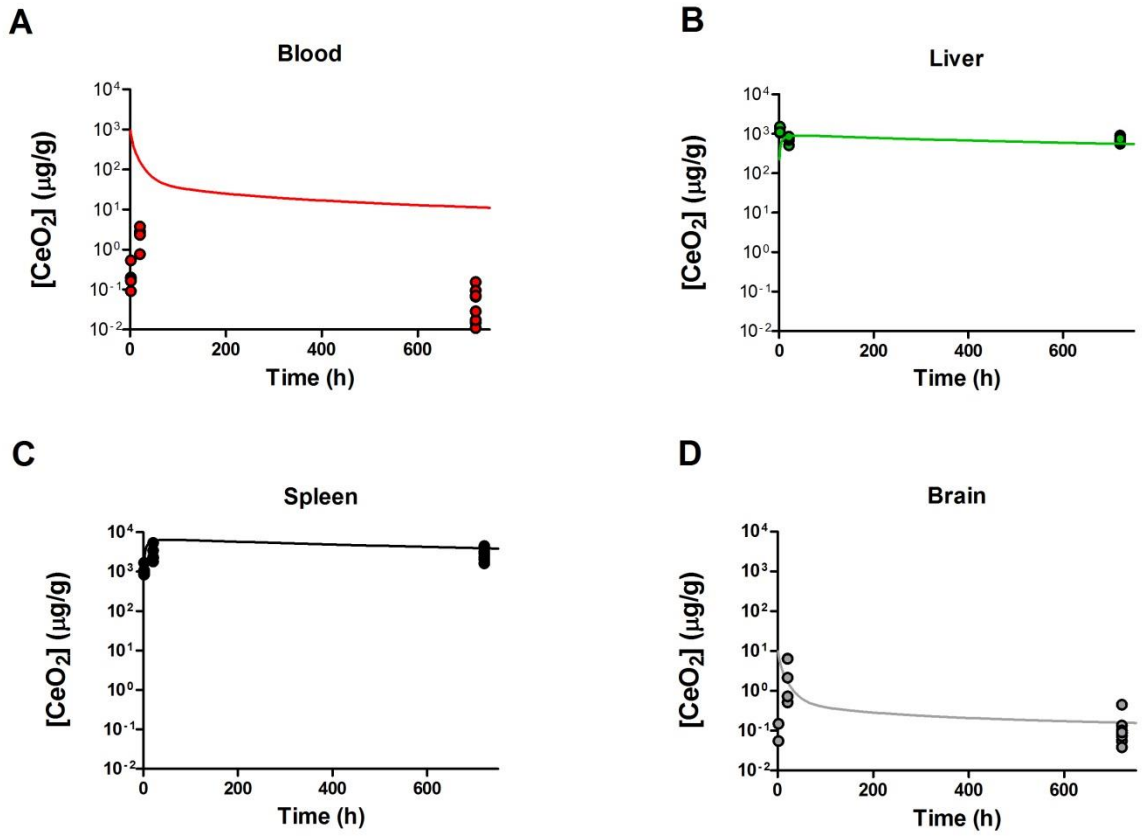


Figure S3. Observed versus simulated concentrations in tissues (Yokel *et al.* 2013)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. (A) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *iv* infusion of 85 mg/kg body weight during 1 h.[2]

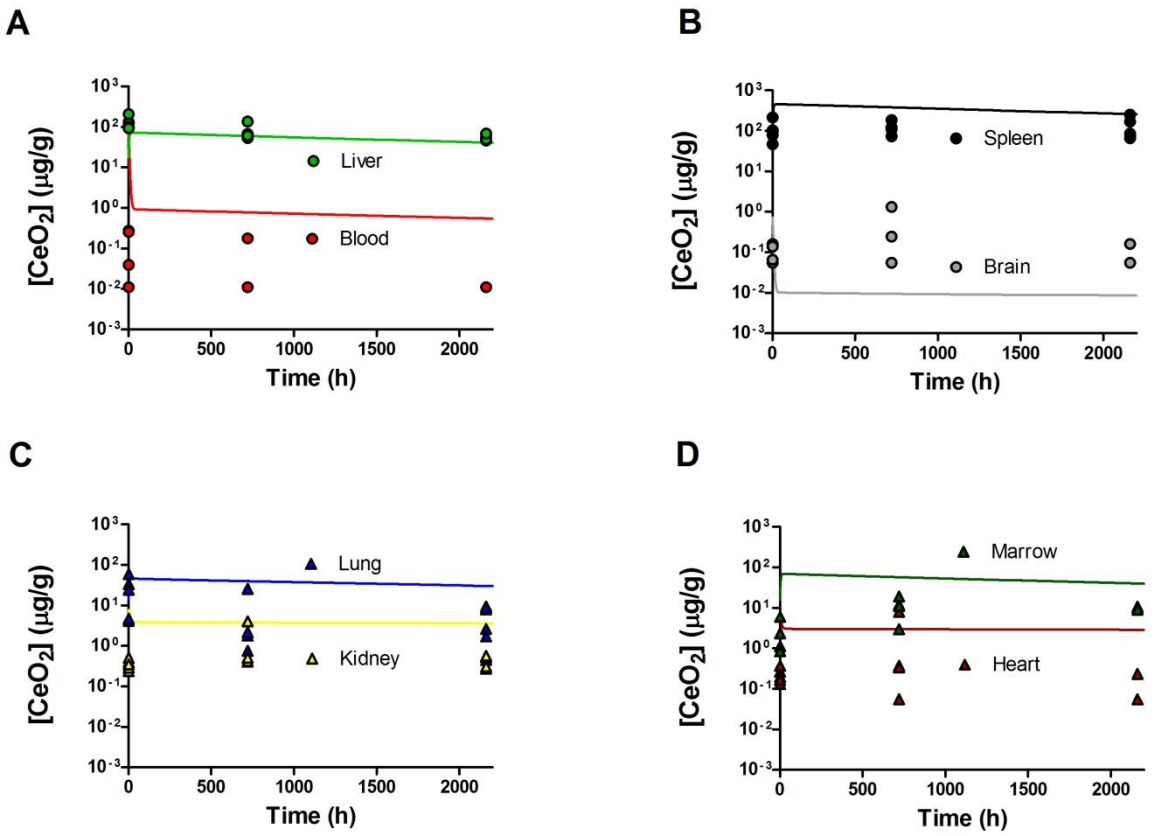


Figure S4. Observed versus simulated concentrations in tissues (Yokel *et al.* 2014)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *iv* infusion of 6 mg/kg body weight during 1 h.[3]

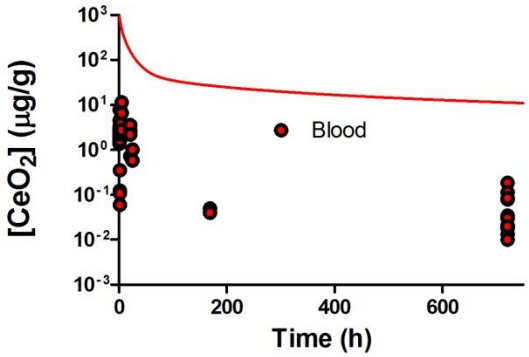


Figure S5. Observed versus simulated concentrations in blood (Dan *et al.* 2012)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in blood following *iv* infusion of 85 mg/kg body weight during 1 h.[5]

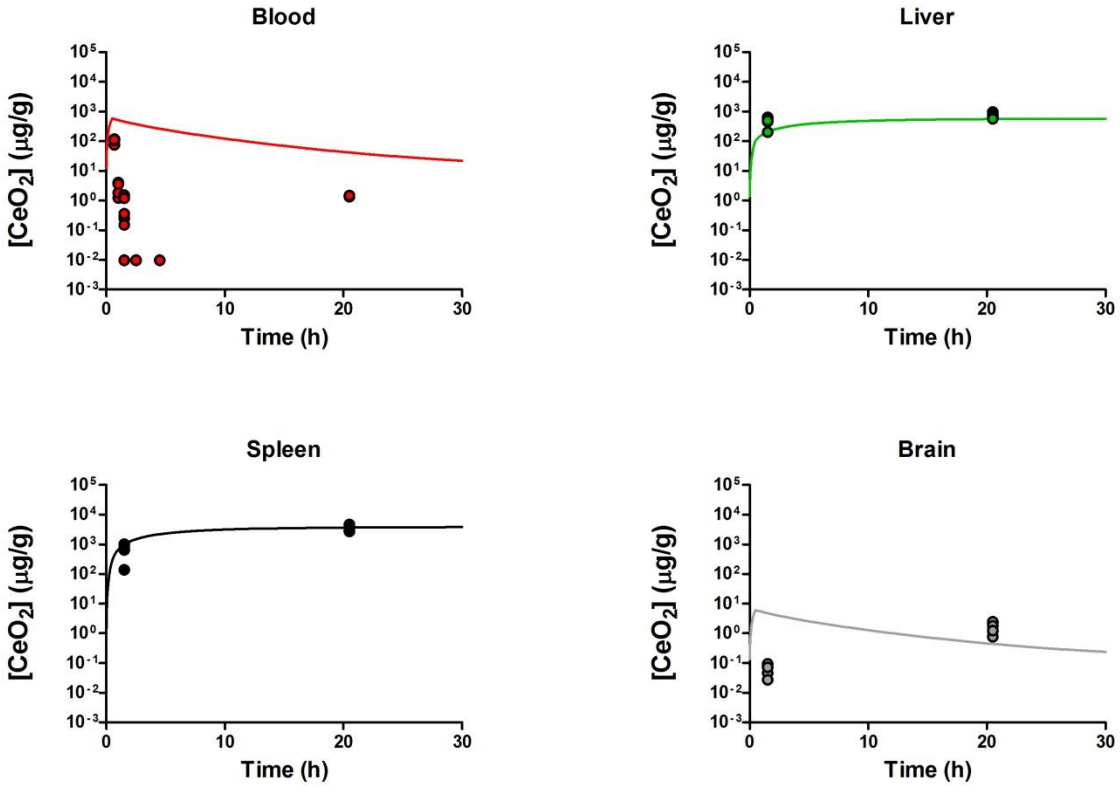


Figure S6. Observed versus simulated concentrations in tissues (Yokel *et al.* 2009 – 50 mg/kg)

Comparison of the 30 nm calibrated PBPK model against independent data sets with 30 nm ceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *iv* infusion of 50 mg/kg during 0.5 h.[6]

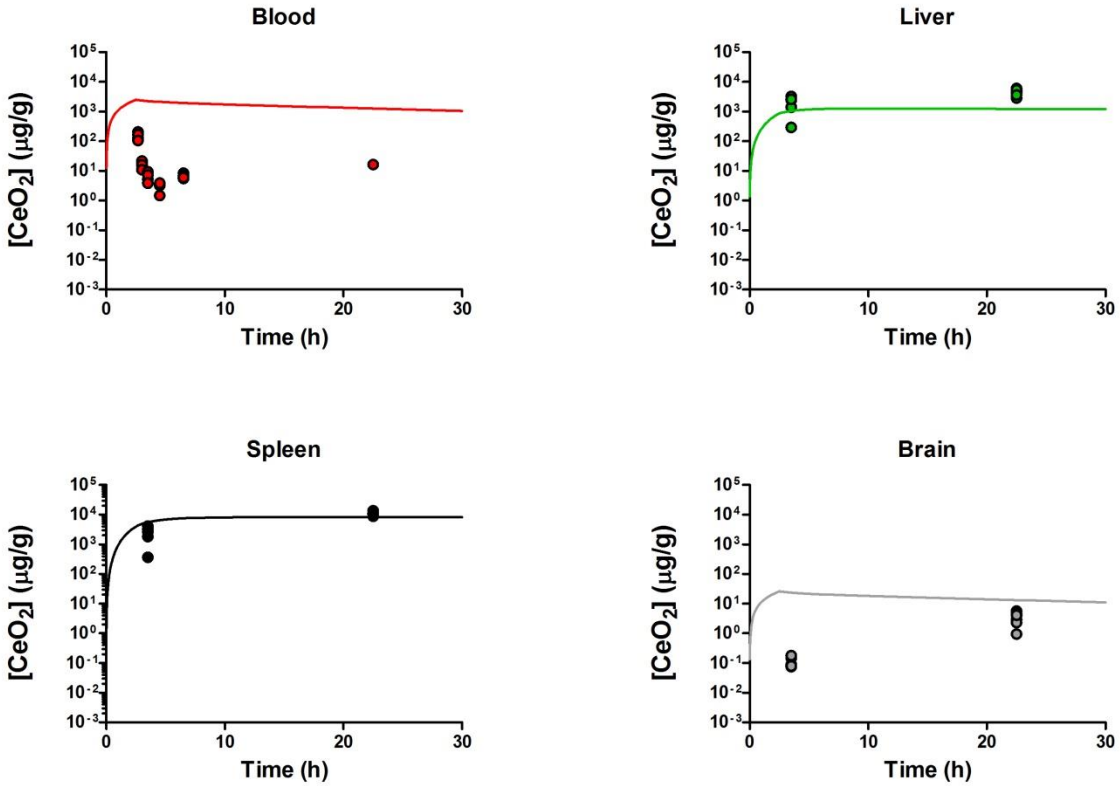


Figure S7. Observed versus simulated concentrations in tissues (Yokel *et al.* 2009 – 250 mg/kg)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. (A-D) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *iv* infusion of 250 mg/kg during 2.5 h.[6]

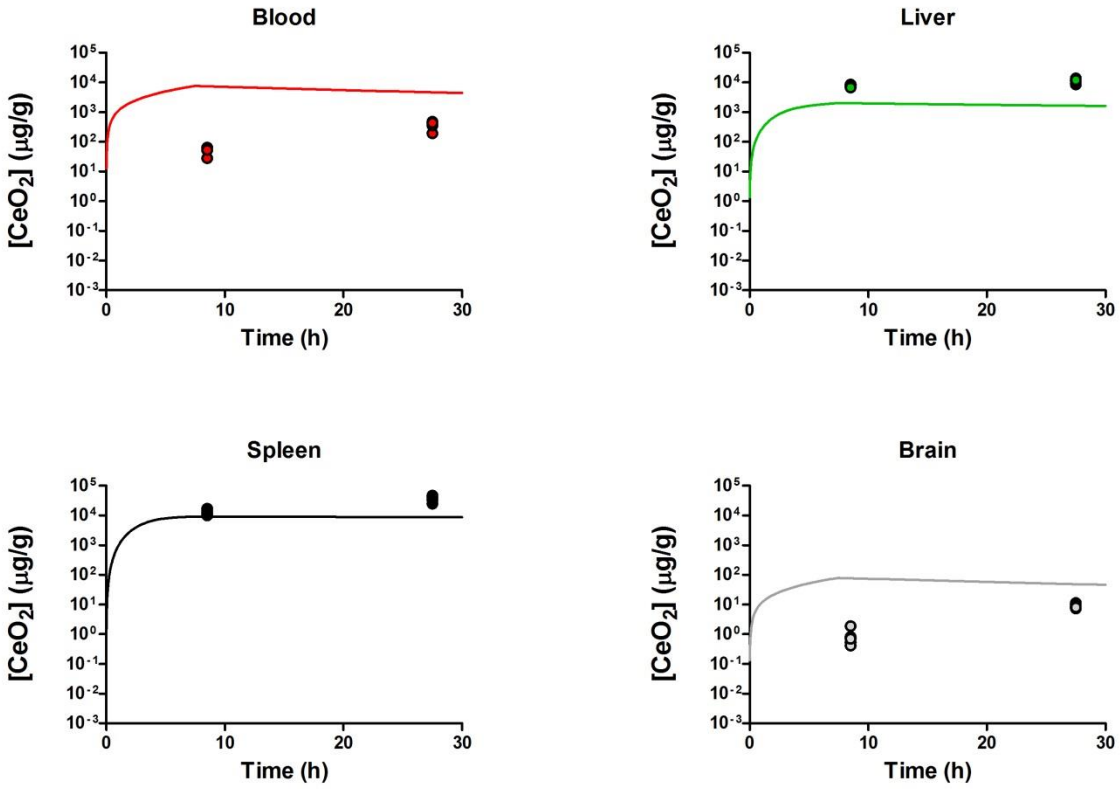


Figure S8. Observed versus simulated concentrations in tissues (Yokel *et al.* 2009 – 750 mg/kg)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *iv* infusion of 750 mg/kg during 7.5 h. [6]

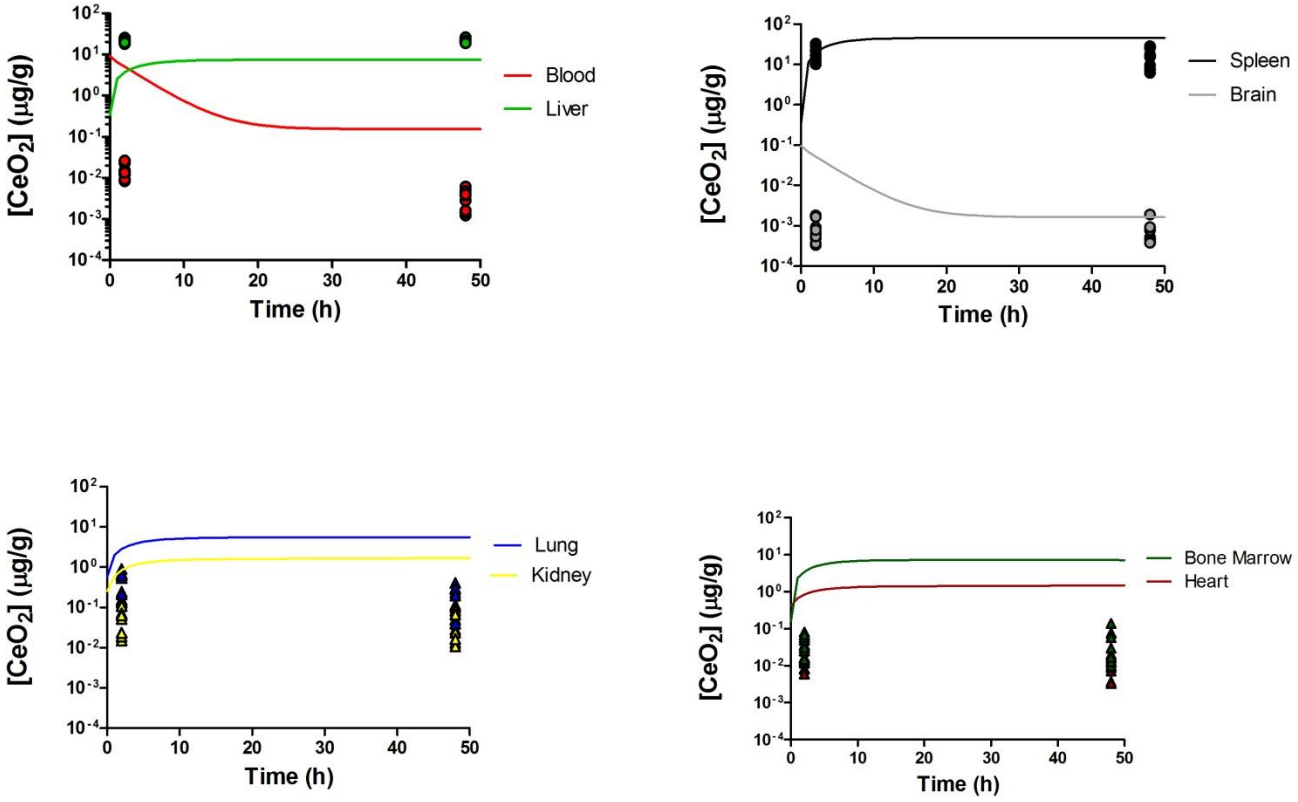


Figure S9. Observed versus simulated concentrations in tissues (Konduru *et al.* 2015 – Silica coated CeO_2)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm ceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following an *iv* bolus dose of 1 mg/kg body weight.[7]

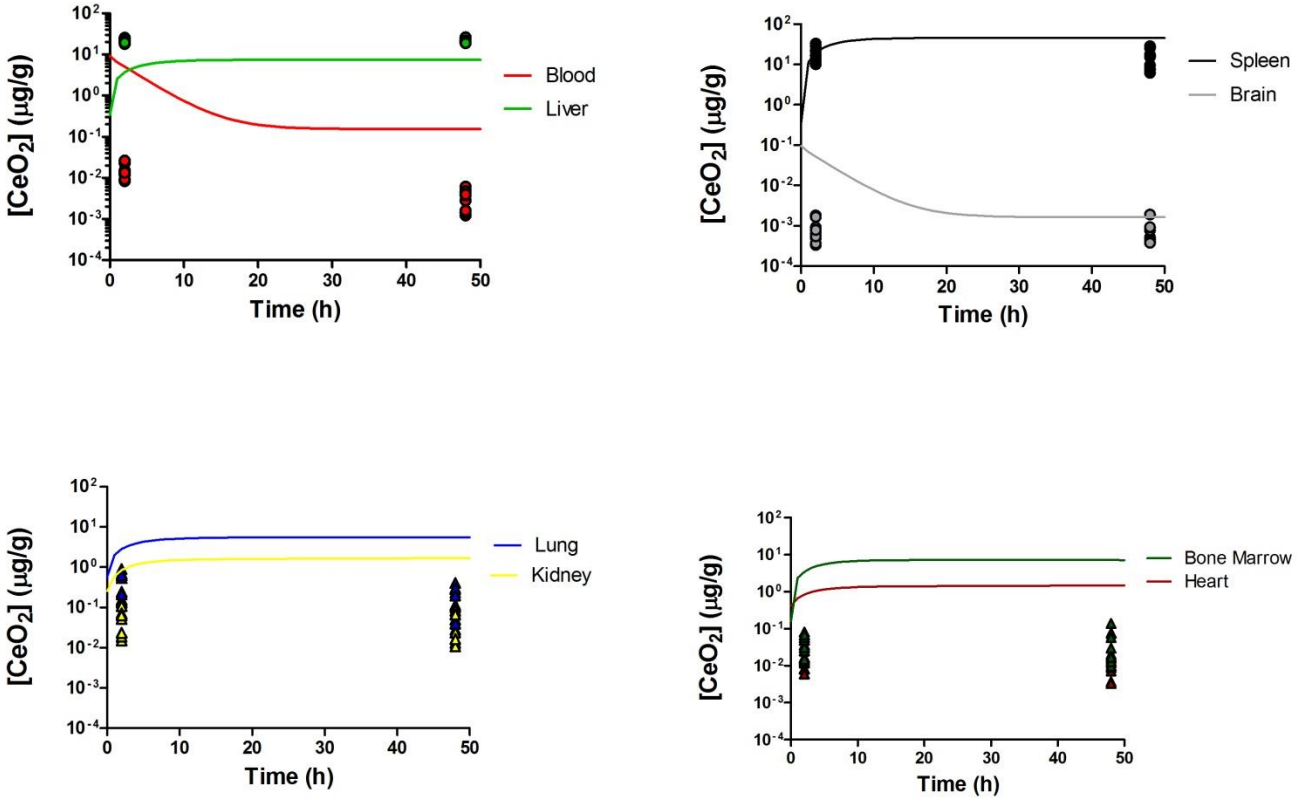


Figure S10. Observed versus simulated concentrations in tissues (Konduru *et al.* 2015 – CeO_2)

Comparison of the 30 nm calibrated PBPK model against independent data set with 30 nm nanoceria. Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following an iv bolus dose of 1 mg/kg body weight.[7]

Comparison of the 5 nm calibrated PBPK to independent data sets with 15 nm ceria

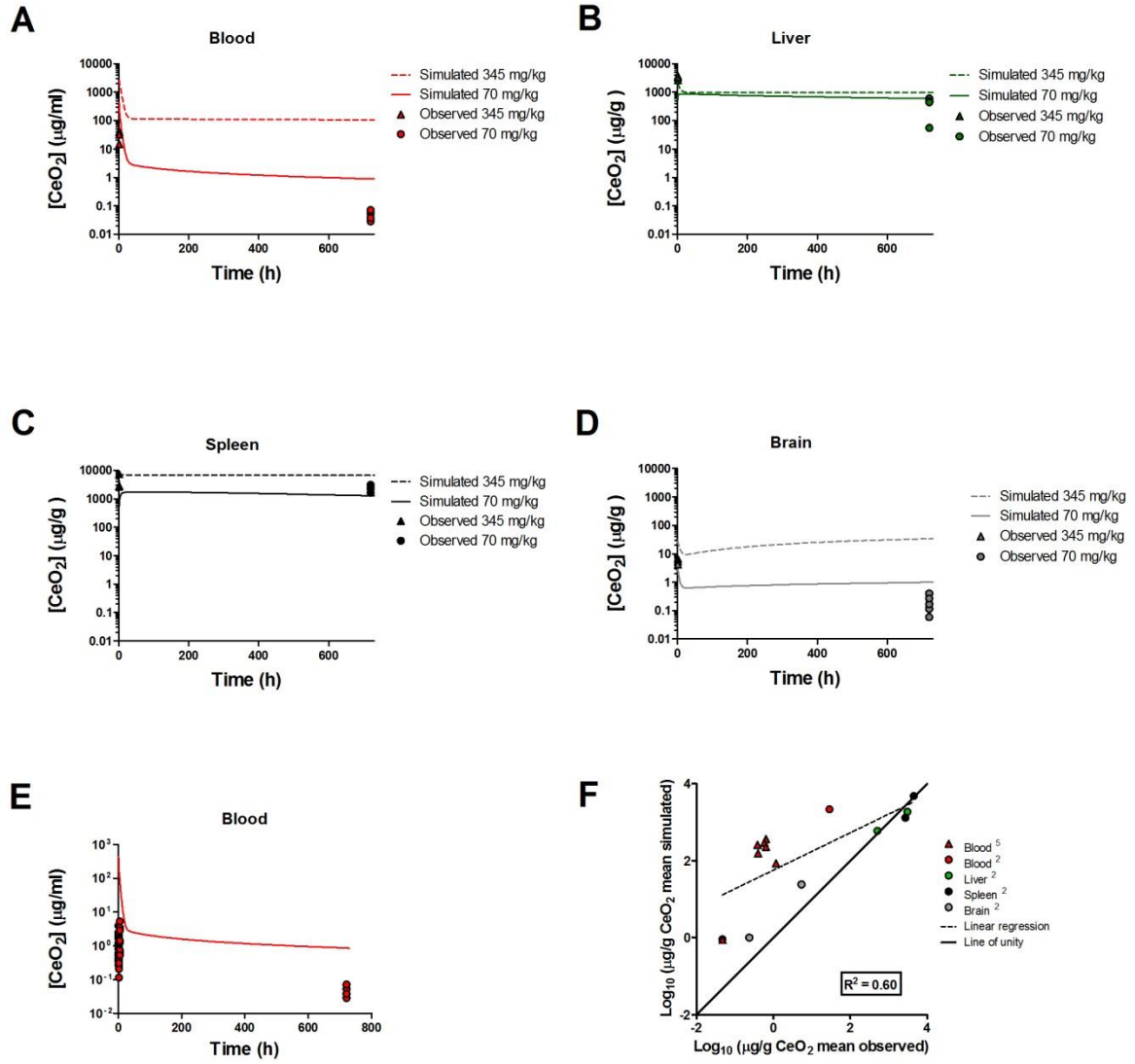


Figure S11. Observed versus simulated concentrations in tissues following administration of 15 nm ceria.

Comparison of the 5 nm calibrated PBPK model against independent data sets with 15 nm ceria. (A-E) Simulated (solid curve) and observed (symbols) time courses of the 15 nm ceria concentration following 1 h *iv* infusion of 70 mg/kg body weight.(A-D)[2] (E)[5] (F) Comparison of logs of simulated and observed mean concentration in different tissues. The line of unity (solid) represents a perfect match and the regression line (R^2, dashed) describes the outcome.

Comparison of the 5 nm calibrated PBPK to independent data sets with 55 nm ceria

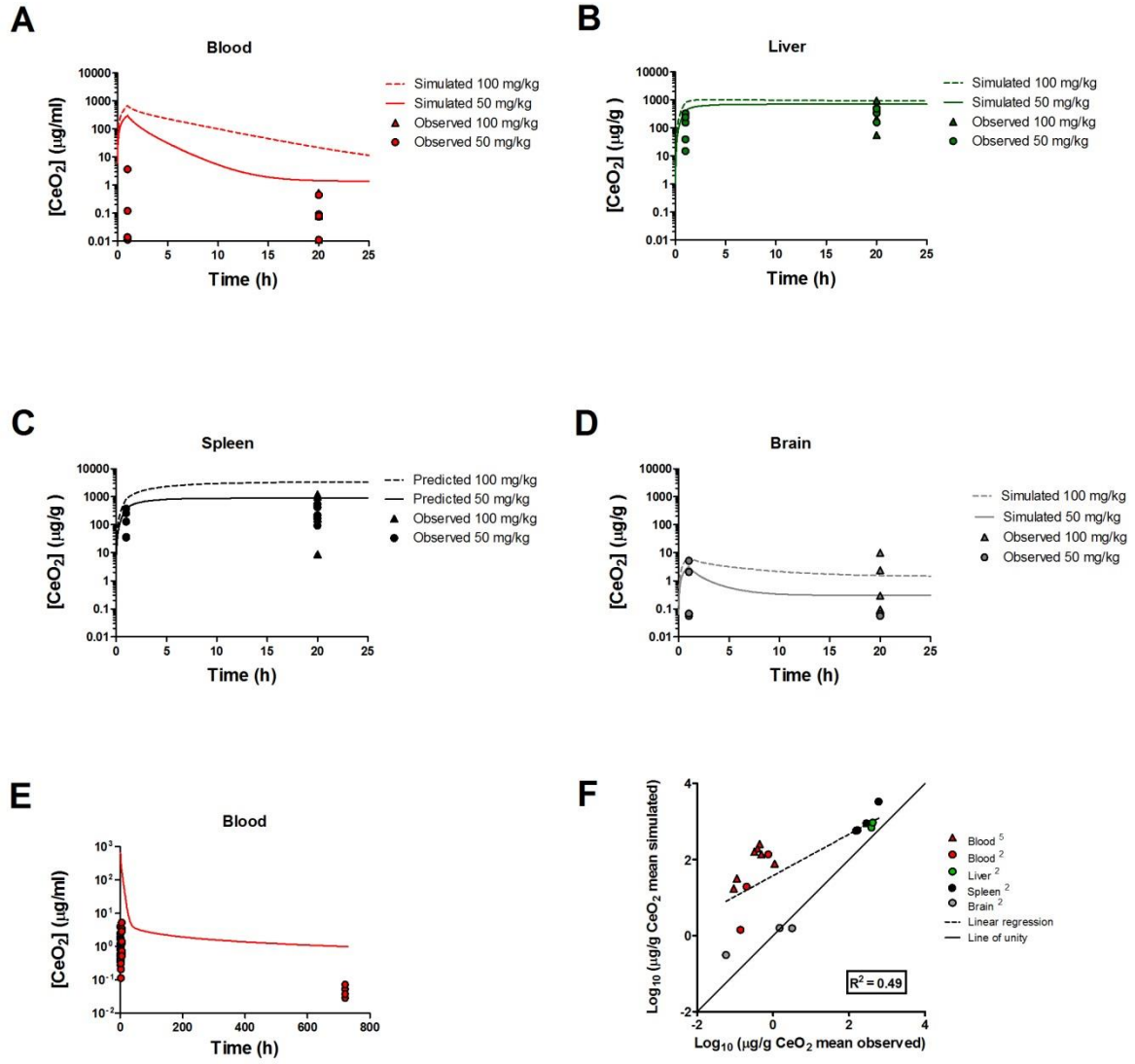


Figure S12. Observed versus simulated concentrations in tissues for 55 nm ceria.

Comparison of the 5 nm calibrated PBPK model against independent data sets with 55 nm ceria.(A-E) Simulated (solid curves) and observed (symbols) time courses of the 55 nm ceria concentration following 1 h *iv* infusion of 50 or 100 mg/kg body weight.(A-D)[2] (E)[5] (F) Comparison of logs of simulated and observed mean concentration in different tissues. The line of unity (solid) represents a perfect match and the regression line (R^2, dashed) describes the outcome.

Tissue: liver concentration ratios

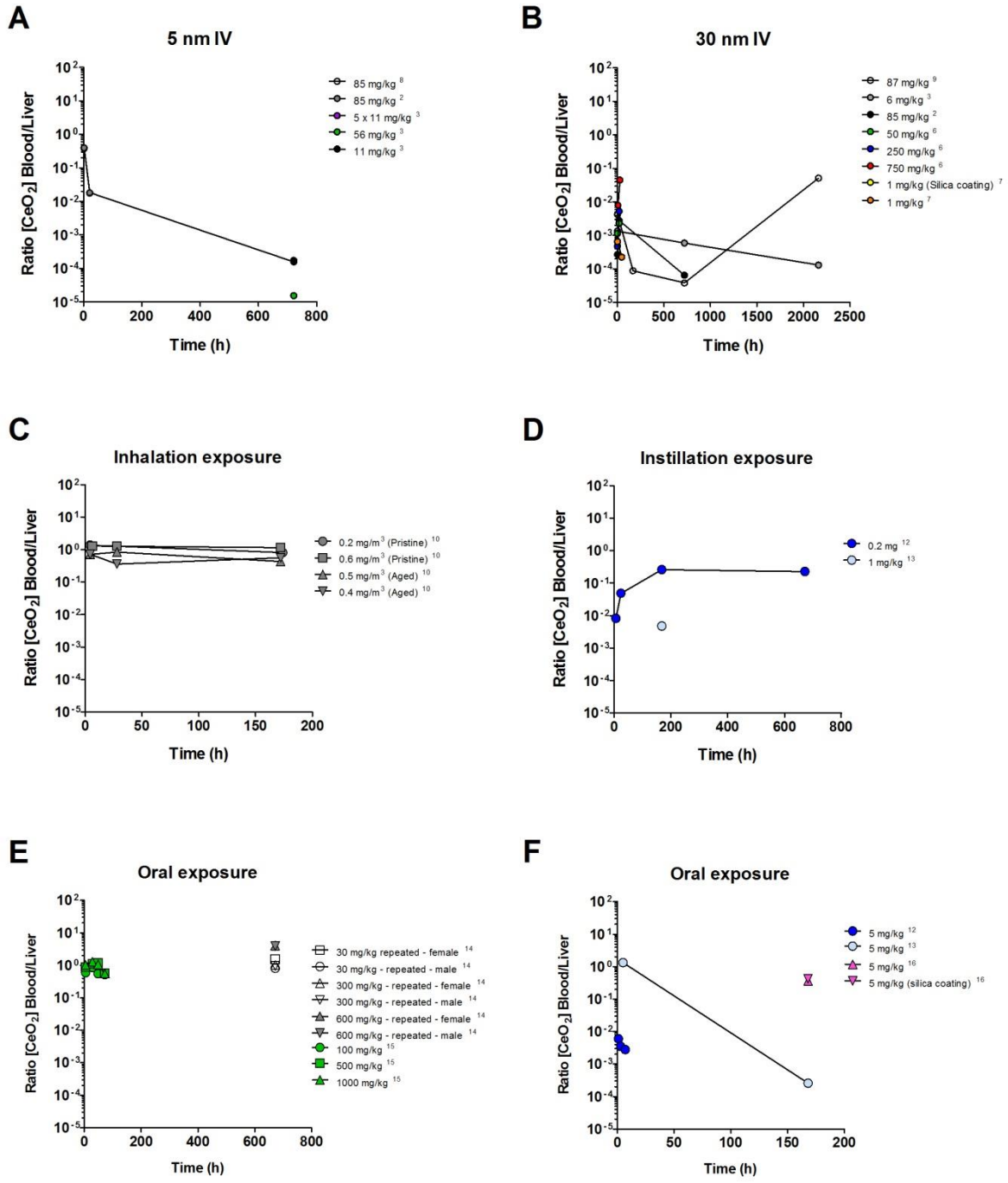


Figure S13. Blood:liver concentration ratios.

Time courses for blood:liver concentration ratios for (A) *iv* administered 5 nm ceria,[2,3,8] (B) *iv* administered 30 nm ceria,[2,3,6,7,9] (C) inhaled nanoceria,[10,11] (D) *it* instilled nanoceria,[12,13] and (E - F) orally administered nanoceria.[12-16]

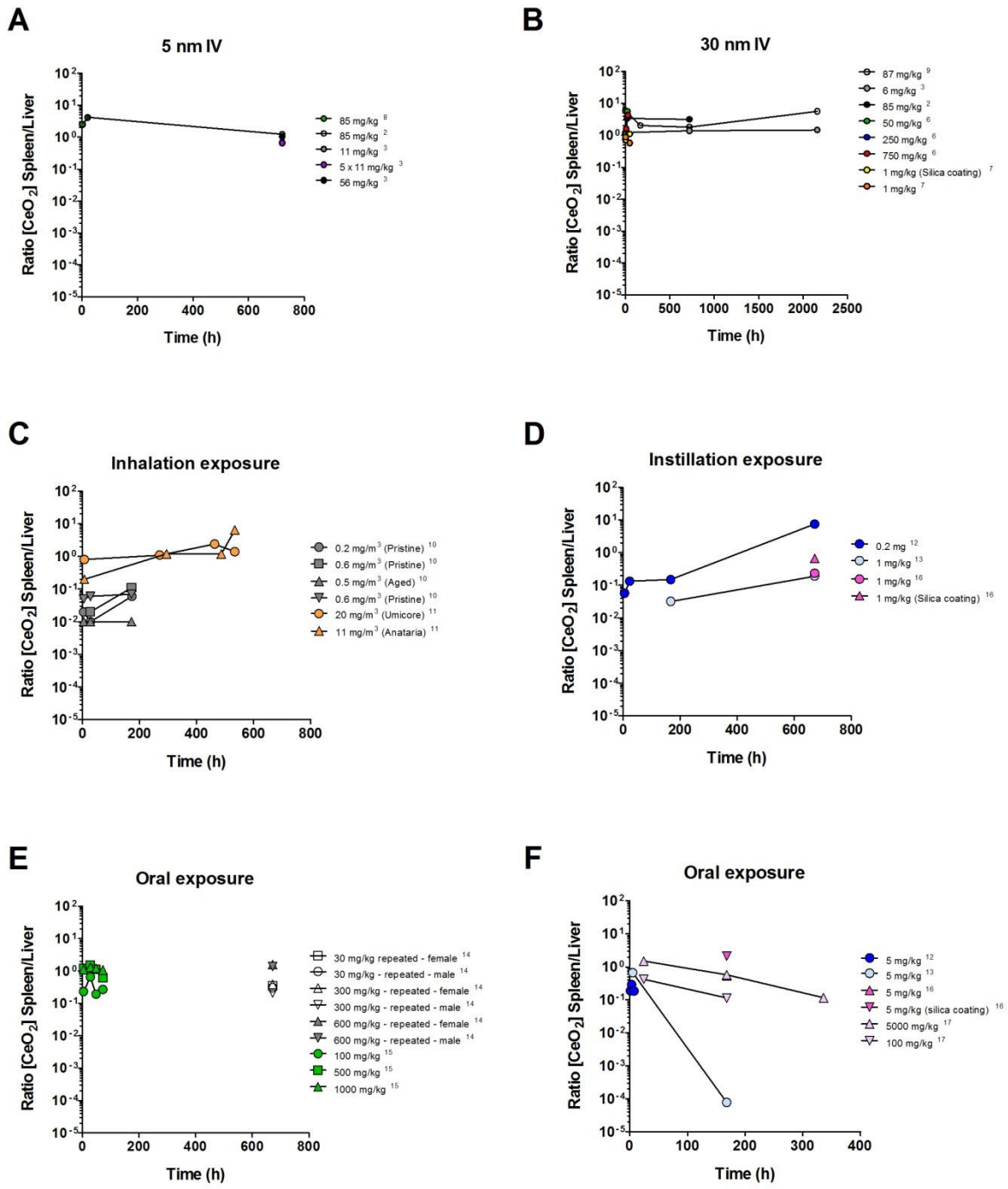


Figure S14. Spleen:liver concentration ratios.

Time courses for spleen:liver concentration ratios for (A) *iv* administered 5 nm ceria, [2,3,8] (B) *iv* administered 30 nm ceria, [2,3,6,7,9] (C) inhaled nanoceria, [10,11] (D) *it* instilled nanoceria, [12,13] and (E -F) orally administered nanoceria. [12-17]

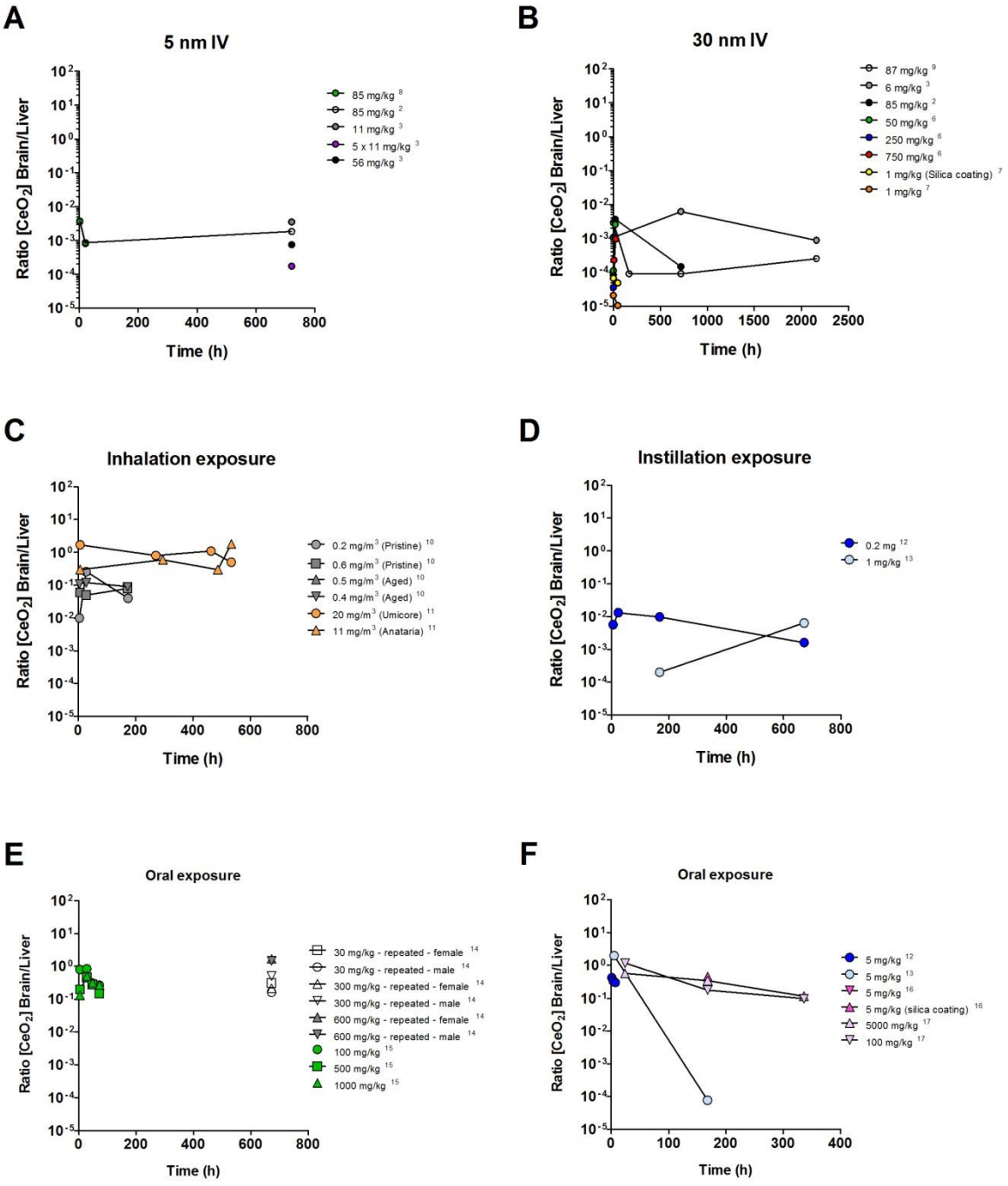


Figure S15. Brain:liver concentration ratios.

Plot of time courses for brain:liver concentration ratios for (A) *iv* administered 5 nm ceria, [2,3,8] (B) *iv* administered 30 nm ceria, [2,3,6,7,9] (C) inhaled nanoceria, [10,11] (D) *it* instilled nanoceria, [12,13] and (E - F) orally administered nanoceria. [12-17]

Calibration oral administration

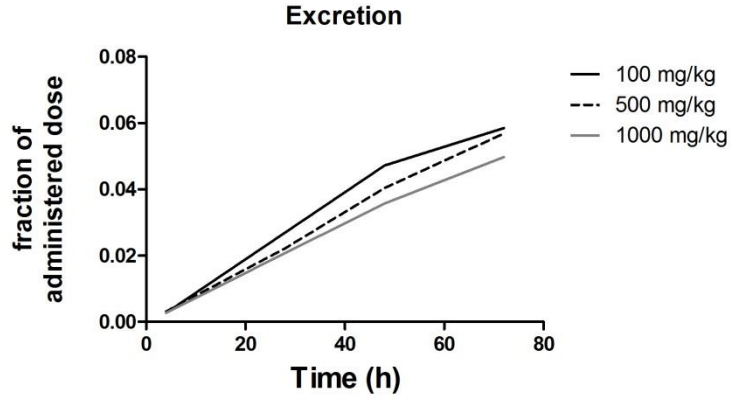


Figure S16. Observed versus simulated concentrations in feces (Kumari *et al.* 2014)

Calibration of the PBPK model against independent data sets with nanoceria was not performed because levels recovered in excretion were only a fraction of the administered dose. Figure presents the time courses of the fraction of the administered dose observed in feces following oral doses of 100, 500 and 1000 mg/kg.[15]

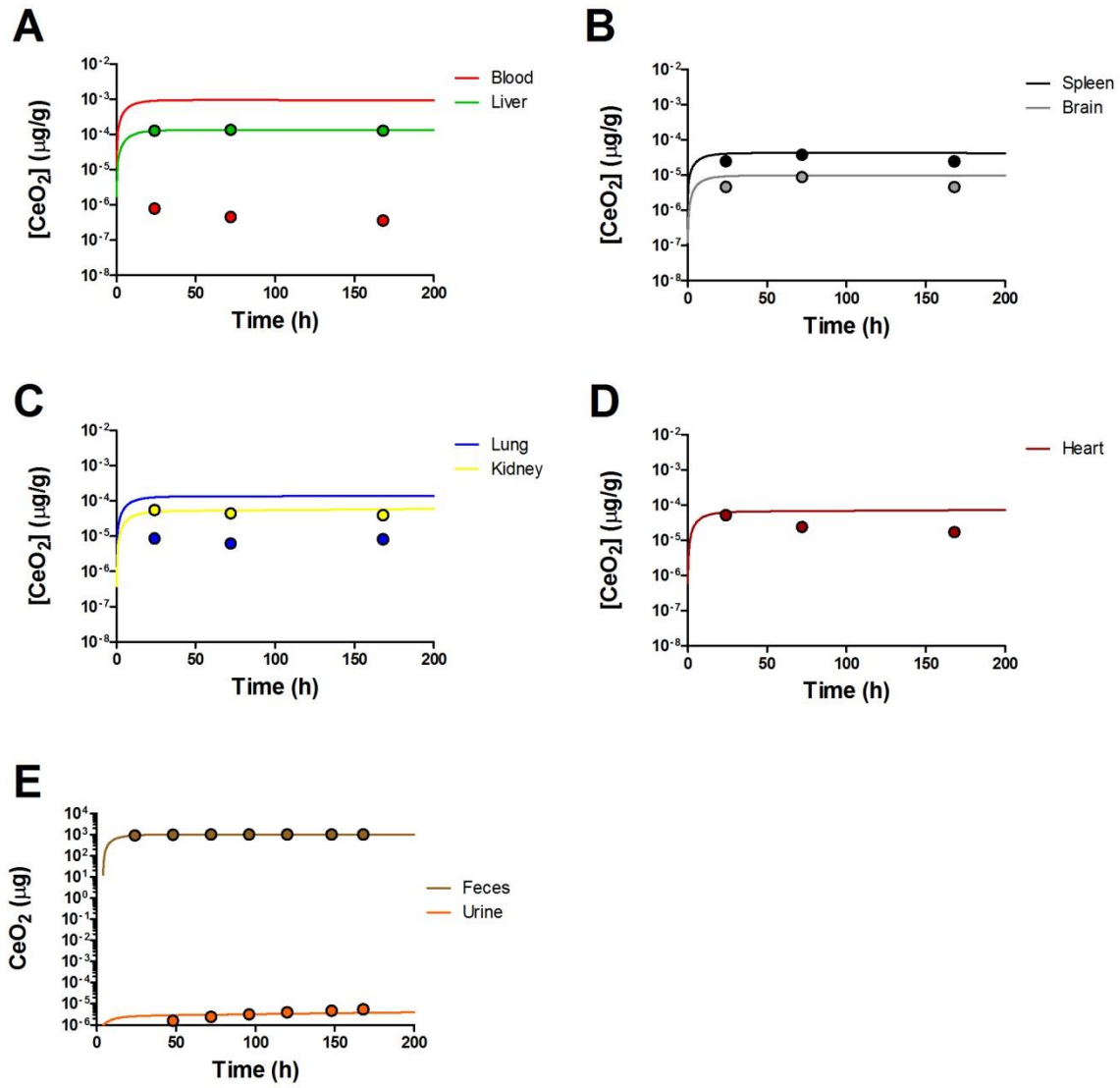


Figure S17. Observed versus simulated concentrations in tissues (He *et al.* 2010)

Calibration of the PBPK model against independent data sets with nanoceria. (A-E) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following an oral dose of 5 mg/kg.[12]

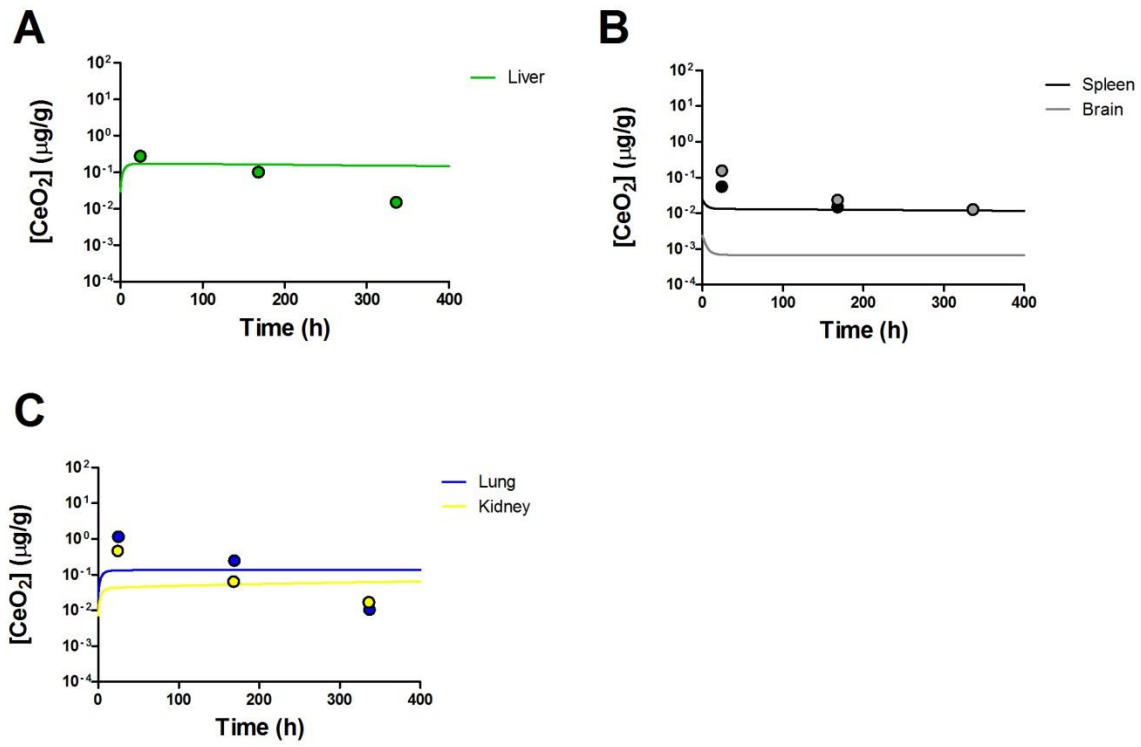


Figure S18. Observed versus simulated concentrations in tissues (Park *et al.* 2009)

Calibration of the PBPK model against independent data sets with nanoceria. (A-C) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following an oral dose of 5000 mg/kg. [17]

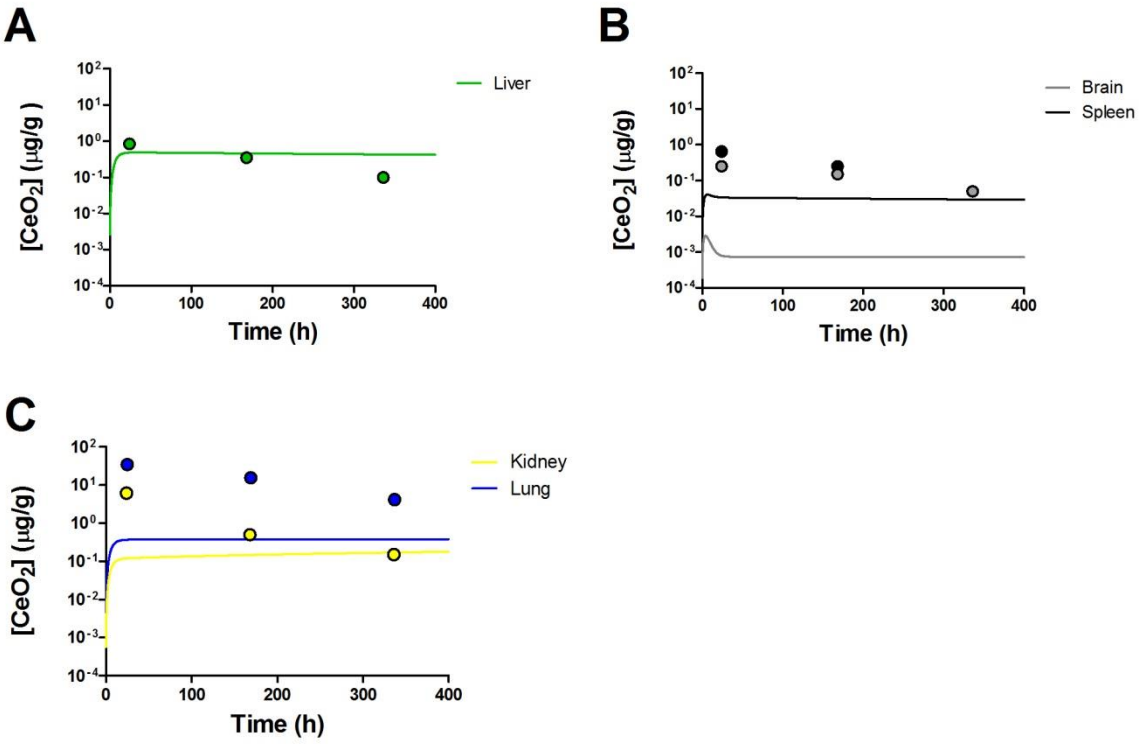


Figure S19. Observed versus simulated concentrations in tissues (Park *et al.* 2009)

Calibration of the PBPK model against independent data sets with nanoceria. (A-C) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following an oral dose of 100 mg/kg.[17]

Calibration inhalation

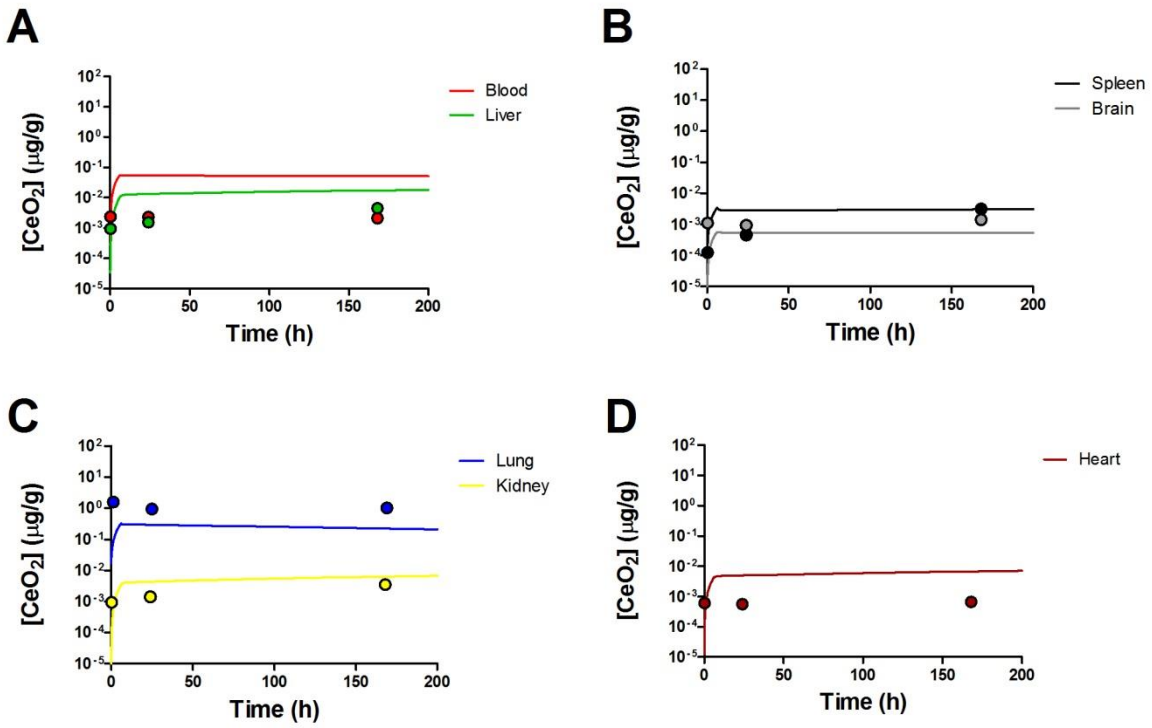


Figure S20. Observed versus simulated concentrations in tissues (Li *et al.* 2016– Pristine)

Calibration of the PBPK model against independent data sets with unaged (pristine) nanoceria. (A-D) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following 6 h nose only inhalation, air concentration 0.6 mg/m^3.[10]

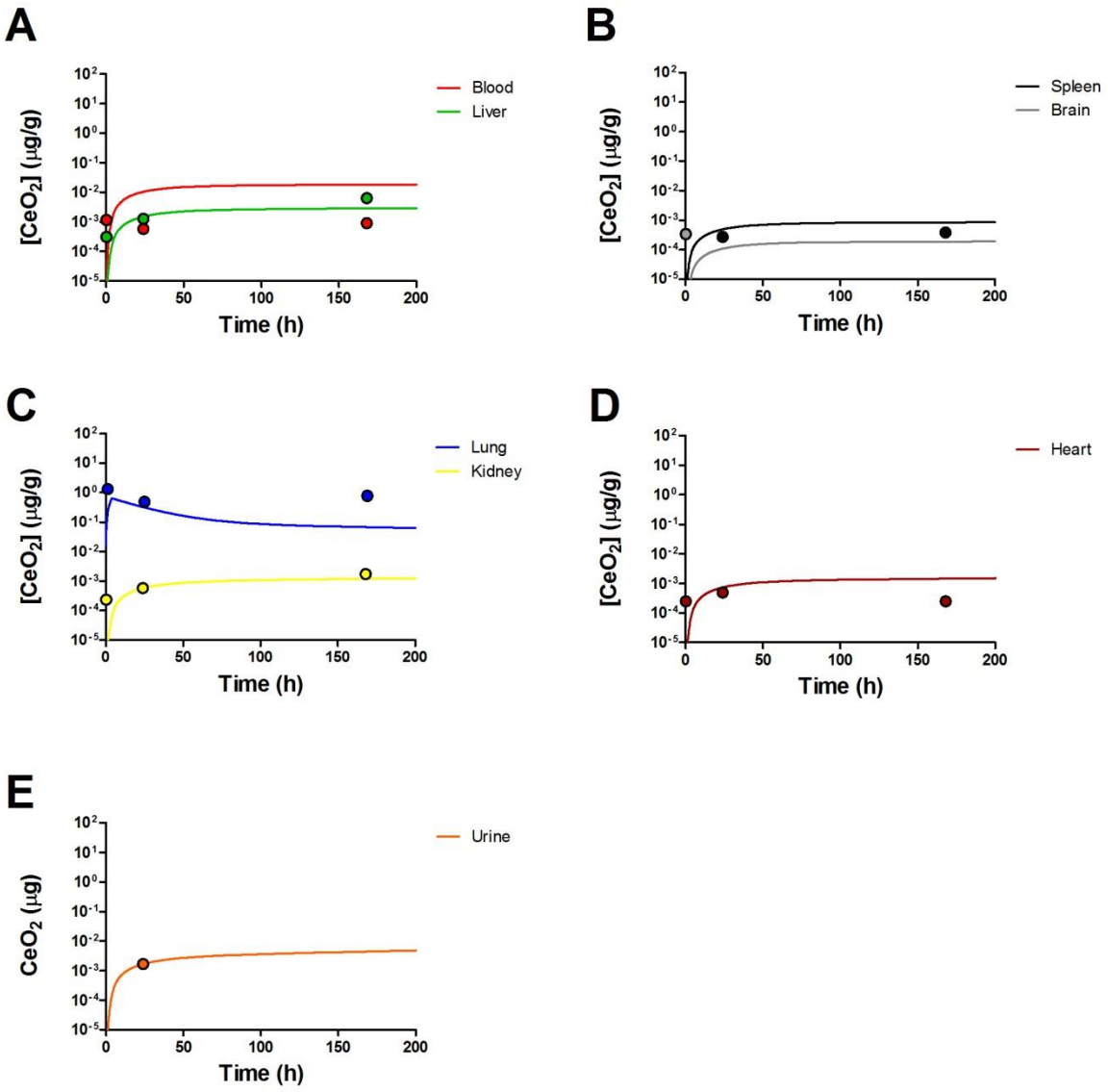


Figure S21. Observed versus simulated concentrations in tissues (Li *et al.* 2016 – Aged)

Calibration of the PBPK model against independent data sets with aged nanoceria. (A-E) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following 4 h nose only inhalation, air concentration 0.4 mg/m^3.[10]

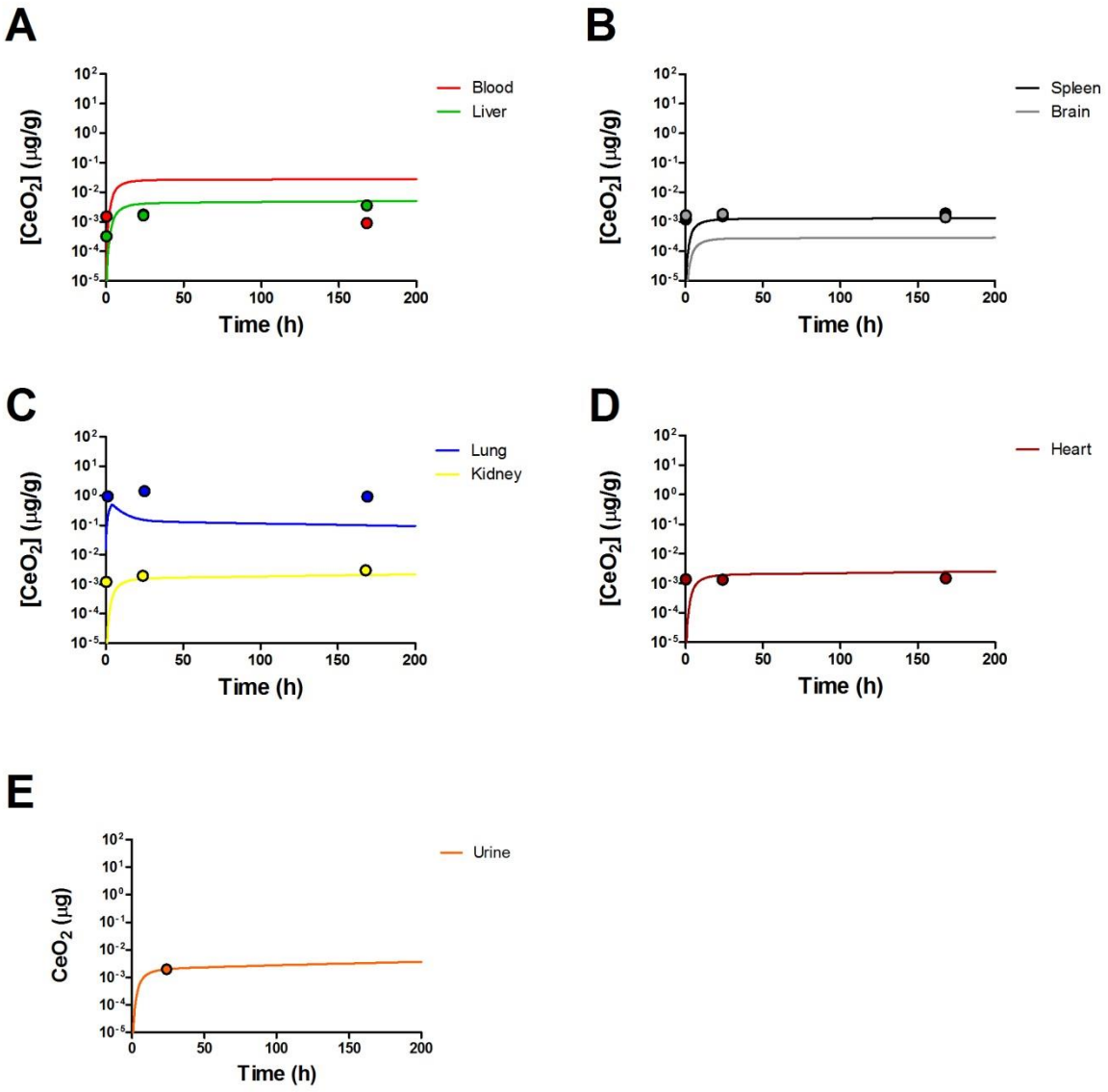


Figure S22. Observed versus simulated concentrations in tissues (Li *et al.* 2016 – Aged)

Calibration of the PBPK model against independent data sets with aged nanoceria. (A-E) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following 4 h nose only inhalation, air concentration 0.5 mg/m^3.[10]

Calibration *it* instillation

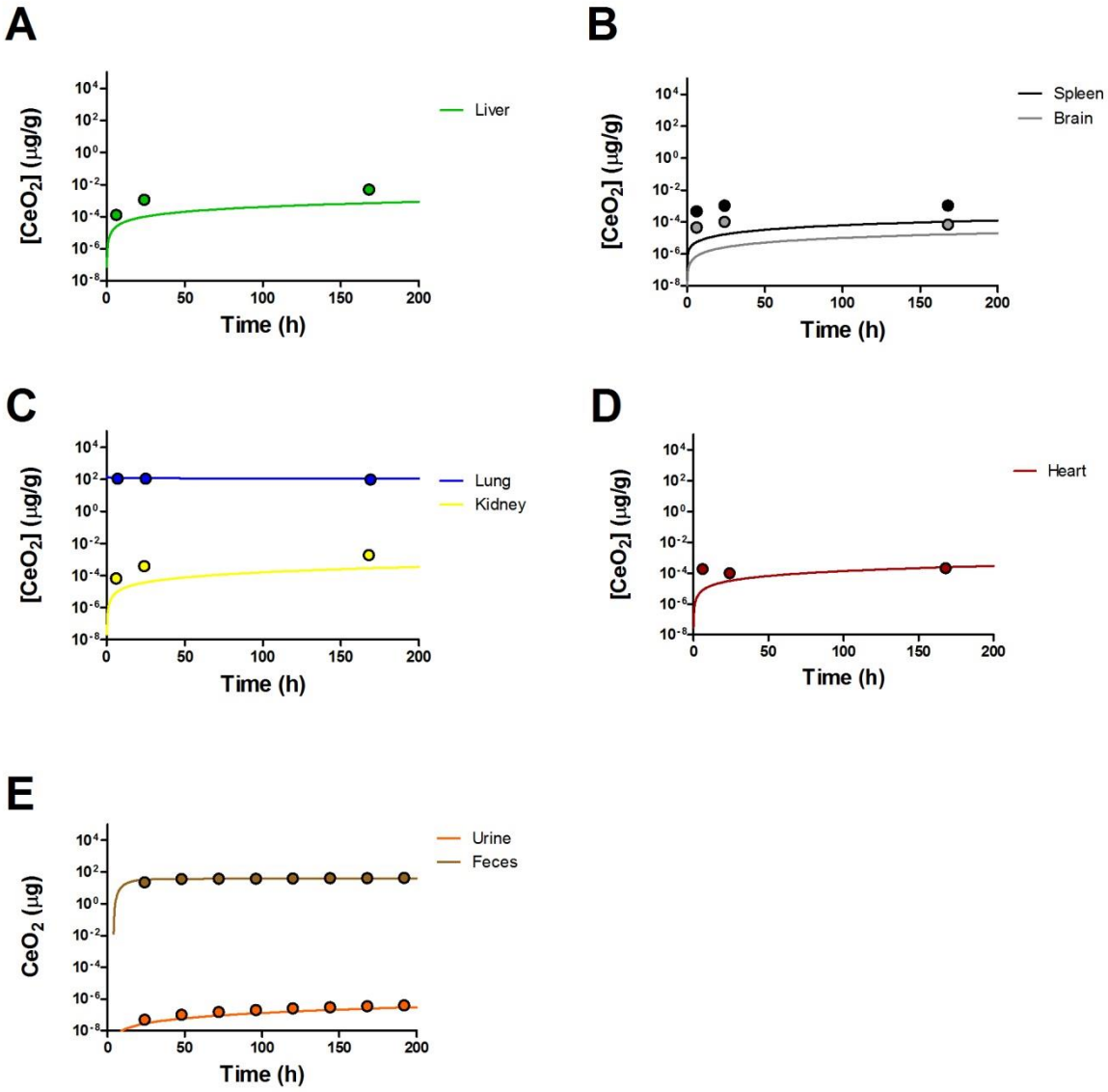


Figure S23. Observed versus simulated concentrations in tissues (He *et al.* 2010)

Calibration of the PBPK model against independent data sets with nanoceria. (A-E) Simulated (solid curves) and observed (symbols) time courses of the nanoceria concentration in different tissues following *it* instillation of 1 mg.[12]

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