Cover Sheet for Supporting Information
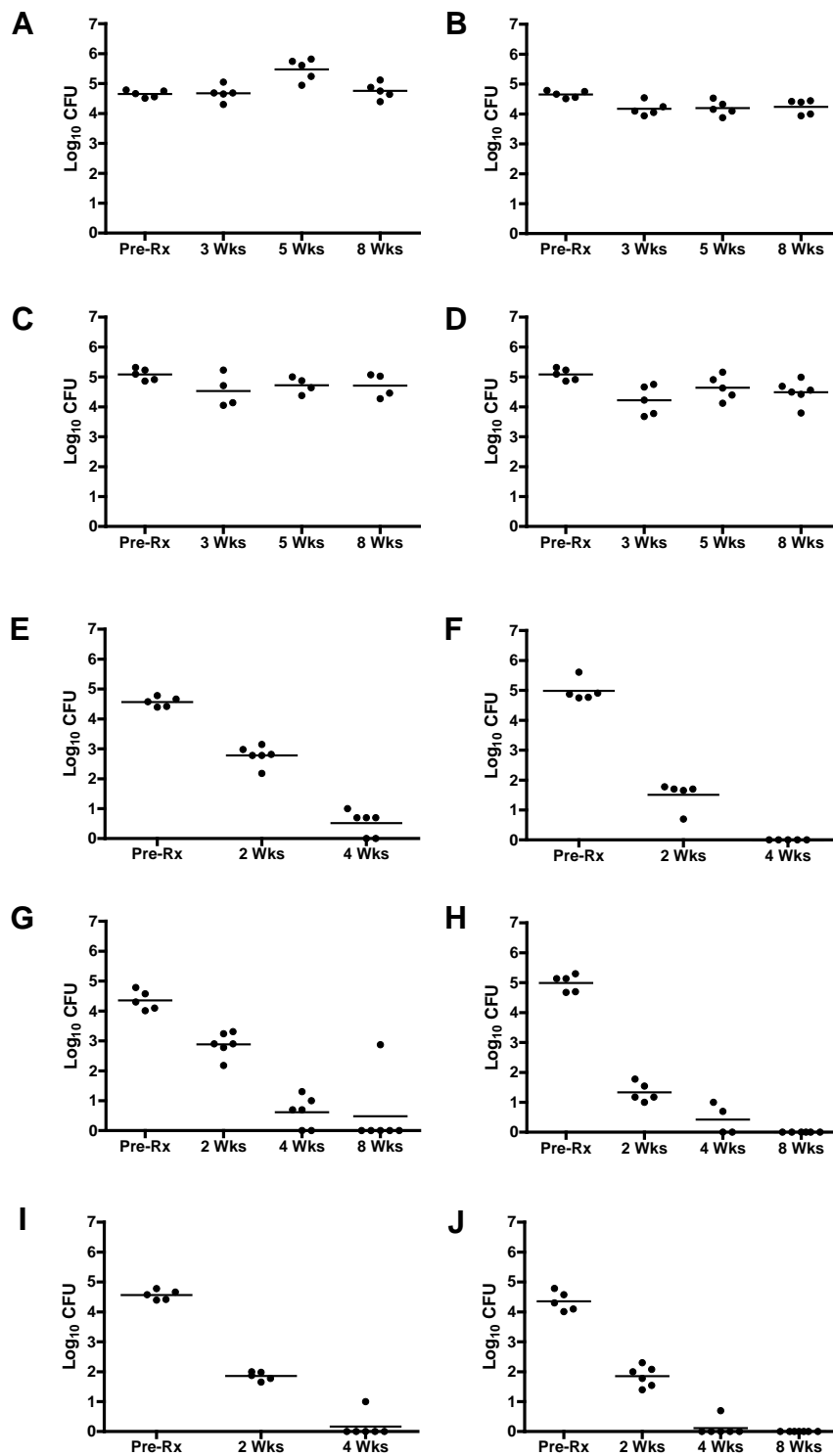
Authors: Scott M. Irwin[1], Brendan Prideaux[2], Edward R. Lyon[1], Matthew D. Zimmerman[2], Elizabeth J. Brooks[1], Christopher A. Schrupp[1], Chao Chen[2], Matthew J. Reichlen[3], Bryce C. Asay[1], Martin I. Voskuil[3], Eric L. Nuermberger[4], Koen Andries[5], Michael A. Lyons[1], Véronique Dartois[2], and Anne J. Lenaerts[1]*

Title: Bedaquiline and Pyrazinamide Treatment Responses are Affected by Pulmonary Lesion heterogeneity in *Mycobacterium tuberculosis* - Infected C3HeB/FeJ Mice
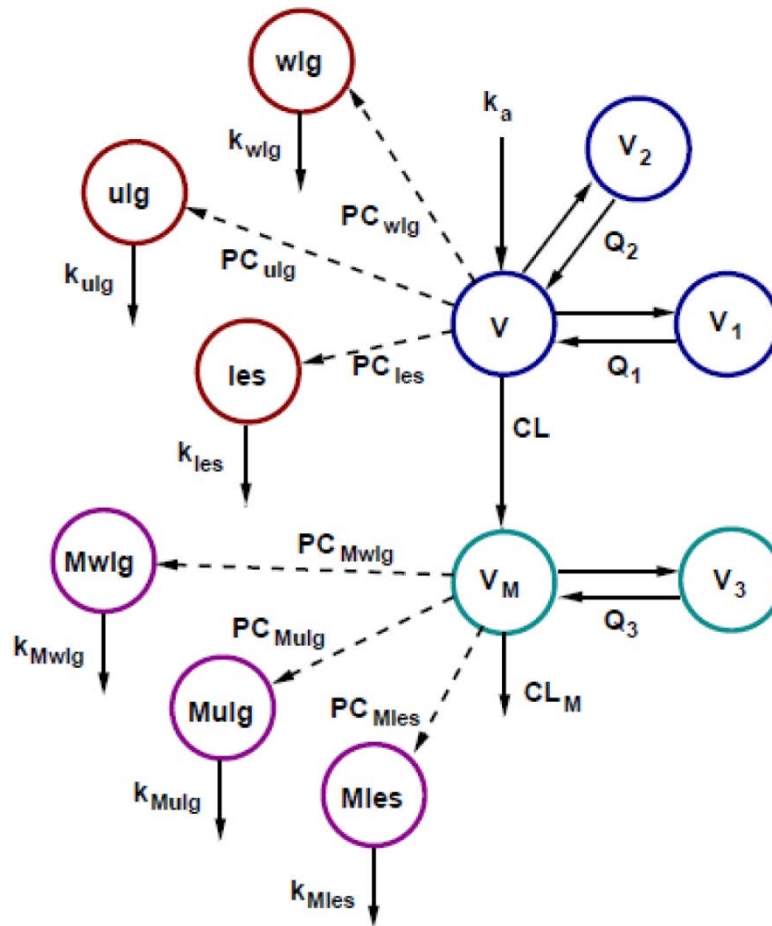
Total Number of Pages: S1-S6

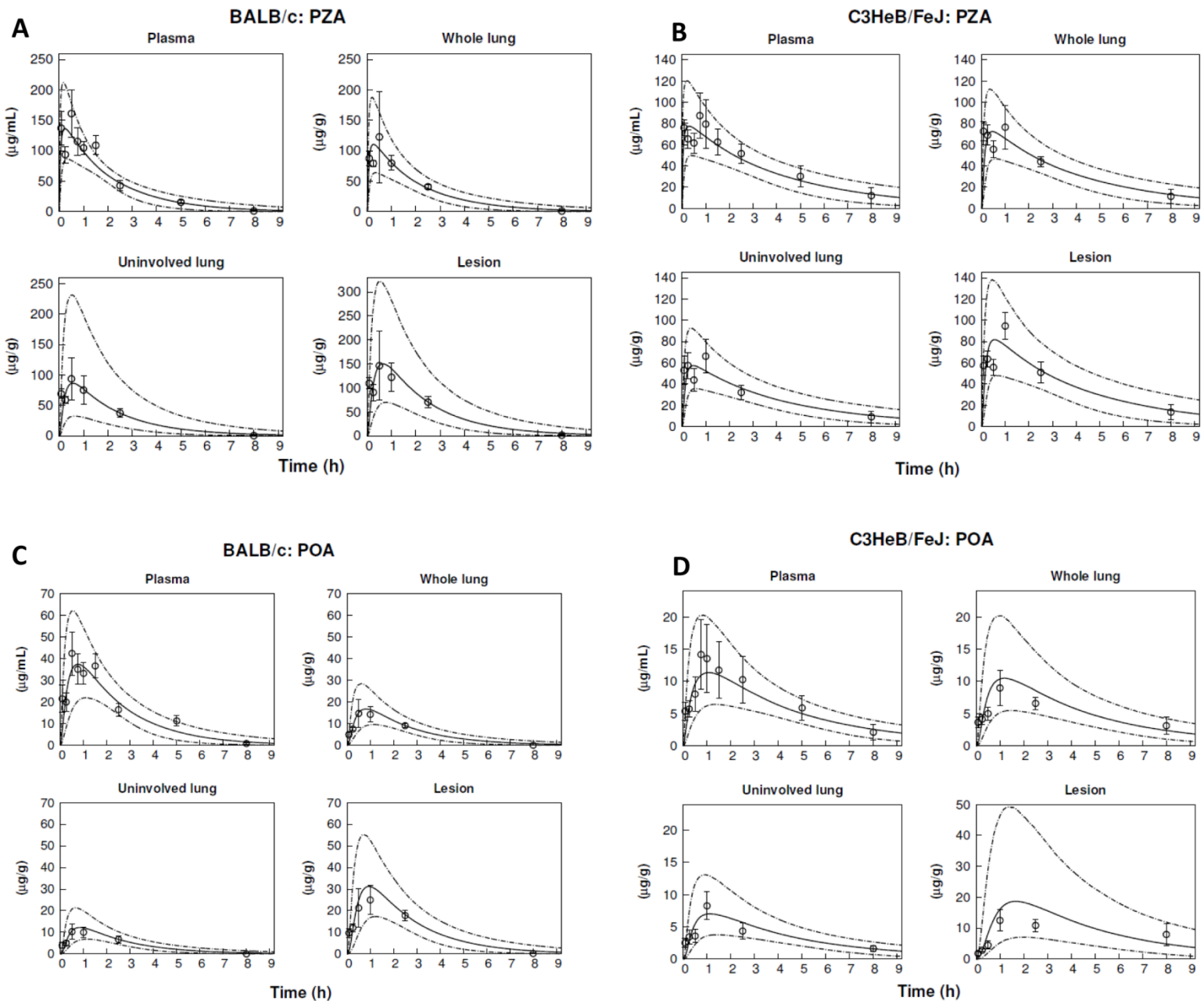Number of Supplemental Figures: 4

Number of Supplemental Tables: 2

Supplemental Figure 1. PZA and BDQ activity were similar in the spleens of BALB/c and C3HeB/FeJ mice. Plots represent $\log_{10}$ CFU determinations from the spleens of individual BALB/c (A, B, E, F, I) or C3HeB/FeJ (C, D, G, H, J) mice. Eight weeks following LDA infection, mice were treated for 3, 5, or 8 weeks with 150 (A, C) or 300 mg/kg (B, D) PZA , or for 2, 4, or 8 weeks with BDQ 10 mg/kg (E, G), BDQ 25 mg/kg (F, H), or BDQ 10 mg/kg and PZA 150 mg/kg in combination (I, J) via oral gavage. Pre-Rx represents untreated mice aerosol infected for 8 weeks following infection.
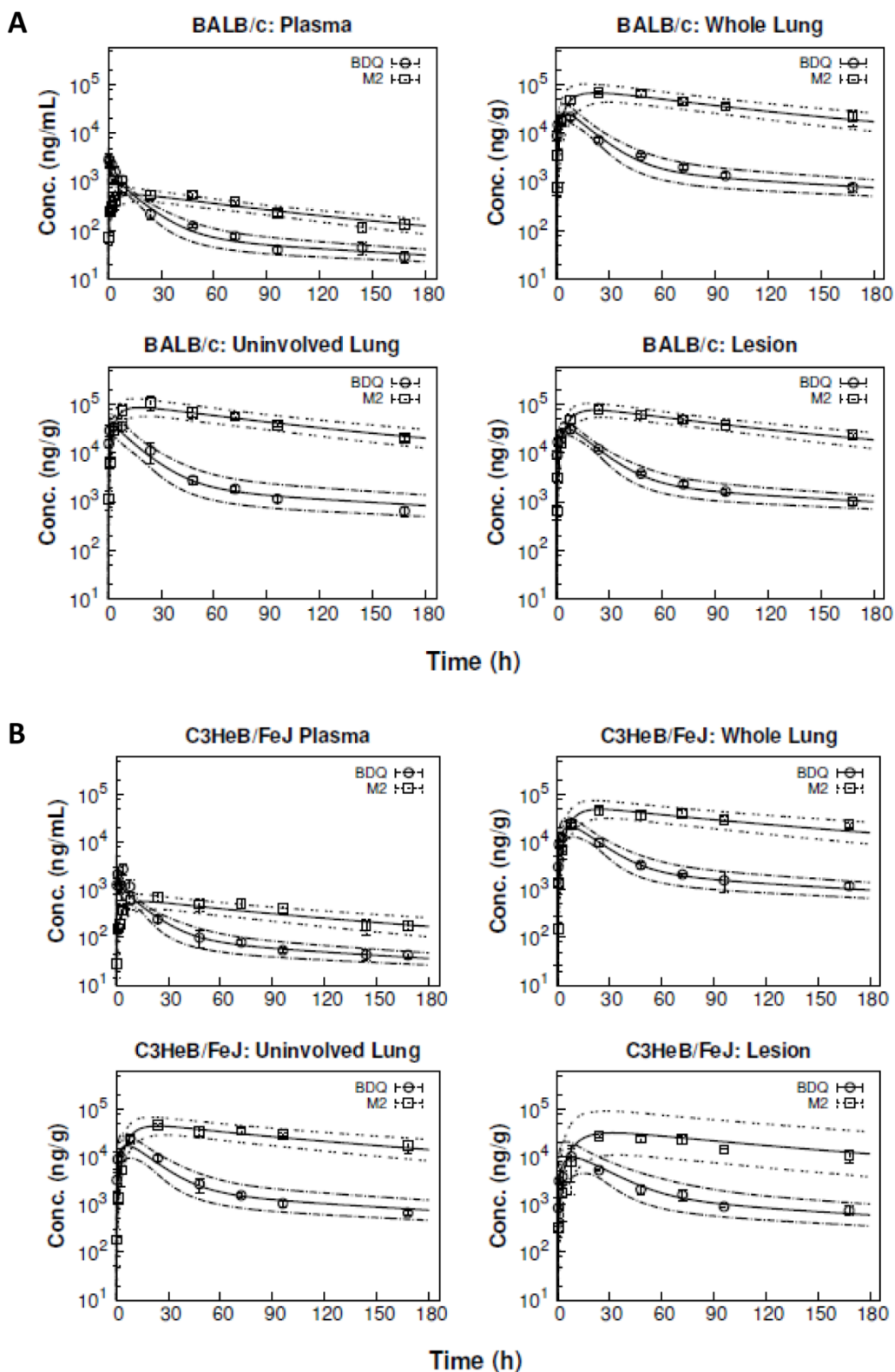
Supplemental Figure 2. BDQ and M2 compartmental structure. BDQ plasma compartments include a central compartment with volume of distribution V and two peripheral compartments, V_1 and V_2. M2 plasma compartments include a central compartment V_M and a single peripheral compartment, V_3. Intercompartmental flow rates are denoted Q_1, Q_2, and Q_3. k_a is the absorption rate constant and CL is BDQ clearance, CL_M is M2 clearance. Tissue compartments are described with elimination rates k_x and penetration coefficients PC_x where $x = \{wlg, ulg, les, Mwlg, Mulg, Mles\}$ for BDQ and metabolite in whole lung, uninvolved lung, and lesion, respectively. PZA plasma compartment includes a central compartment with volume of distribution V, with no peripheral compartments. POA plasma compartment includes a central compartment V_M with no peripheral compartments. Tissue compartments are described with elimination rates k_x and penetration coefficients PC_x where $x = \{wlg, ulg, les, Mwlg, Mulg, Mles\}$ for PZA and POA in whole lung, uninvolved lung, and lesion, respectively.

Supplemental Figure 3. MC simulations of plasma and lung tissue concentration-time profiles.
MC simulations (dashed lines) are shown together with corresponding experimental data (mean ± SD) for PZA (A, B) and POA (C, D) in BALB/c (A, C) and C3HeB/FeJ (B, D) mice following a single 150 mg/kg PZA oral dose. Solid and dashed lines are simulations corresponding to the median (solid) and bounds determined by the 5th and 95th percentiles (dashed).

Supplemental Figure 4. MC simulations of plasma and lung tissue concentration-time profiles.
MC simulations (dashed lines) are shown together with corresponding experimental data (mean ± SD) of BDQ and M2 in BALB/c (A) and C3HeB/FeJ (B) mice following a single 25 mg/kg oral BDQ dose. Solid and dashed lines are simulations corresponding to median (solid) and bounds determined by the 5th and 95th percentiles (dashed).

Parameter (units)	BALB/c		C3HeB/FeJ	
	GM (% RSD)	GSD (% RSD)	GM (% RSD)	GSD (% RSD)
k_a (h^{-1})	18.48 (10.73)	1.90 (14.06)	22.09 (9.28)	2.21 (10.11)
CL (L/h/kg)	0.46 (5.40)	1.13 (5.54)	0.41 (6.81)	1.25 (5.82)
V (L/kg)	0.96 (6.06)	1.34 (5.49)	1.77 (5.35)	1.32 (4.65)
CL_M (L/h/kg)	1.28 (6.46)	1.16 (6.15)	2.29 (7.26)	1.20 (7.10)
V_M (L/kg)	0.38 (14.04)	1.97 (8.84)	0.78 (16.06)	1.77 (10.58)
k_{wlg} (h^{-1})	70.32 (14.61)	1.68 (15.08)	14.83 (8.02)	1.69 (13.87)
PC_{wlg}	0.81 (5.68)	1.20 (6.20)	0.96 (3.51)	1.06 (5.23)
k_{ulg} (h^{-1})	6.17 (8.77)	1.67 (14.72)	13.59 (8.66)	1.63 (15.00)
PC_{ulg}	0.74 (10.77)	1.72 (9.57)	0.76 (4.77)	1.15 (5.09)
k_{les} (h^{-1})	4.66 (8.40)	1.77 (13.23)	8.80 (8.85)	1.45 (13.52)
PC_{les}	1.34 (9.49)	1.48 (10.58)	1.10 (4.89)	1.11 (4.66)
k_{Mwlg} (h^{-1})	23.08 (11.05)	1.41 (13.89)	13.16 (8.94)	1.72 (13.84)
PC_{Mwlg}	0.45 (5.35)	1.12 (6.16)	0.93 (5.92)	1.22 (7.45)
k_{Mulg} (h^{-1})	16.06 (9.53)	1.65 (13.97)	18.09 (8.82)	1.69 (14.62)
PC_{Mulg}	0.33 (6.35)	1.17 (6.43)	0.62 (5.67)	1.16 (6.75)
k_{Mles} (h^{-1})	8.96 (8.74)	1.90 (12.25)	2.63 (10.25)	1.53 (14.55)
PC_{Mles}	0.86 (6.54)	1.19 (8.62)	1.78 (7.47)	1.44 (10.62)

Supplemental Table 1. Summary statistics of compartmental model parameter distributions for

PZA and POA in BALB/c and C3HeB/FeJ mice. Population geometric mean (GM) and

population geometric standard deviation (GSD) of each parameter calculated from the

corresponding posterior marginal distributions. Uncertainty of estimate provided as percent

relative standard deviation (% RSD) calculated from 10,000 MCMC samples.

Parameter (units)	BALB/c		C3HeB/FeJ	
	GM (% RSD)	GSD (% RSD)	GM (% RSD)	GSD (% RSD)
k_a (h^{-1})	5.39 (9.14)	1.67 (14.41)	4.32 (14.82)	1.77 (14.65)
CL (L/h/kg)	0.71 (4.53)	1.06 (3.64)	0.71 (5.35)	1.07 (3.78)
V (L/kg)	6.27 (10.25)	1.30 (7.67)	7.90 (10.12)	1.55 (9.14)
Q_1 (L/h/kg)	3.63 (10.59)	1.64 (13.78)	5.37 (9.31)	1.72 (14.61)
V_1 (L/kg)	6.46 (10.93)	1.44 (10.56)	7.51 (14.04)	1.58 (12.73)
Q_2 (L/h/kg)	0.41 (6.94)	1.14 (6.09)	0.59 (8.63)	1.18 (6.79)
V_2 (L/kg)	41.86 (13.89)	1.22 (10.20)	61.71 (12.38)	1.22 (9.82)
CL_M (L/h/kg)	0.35 (4.60)	1.09 (5.54)	0.27 (8.56)	1.17 (6.74)
V_M (L/kg)	8.52 (7.98)	1.21 (7.16)	8.98 (11.70)	1.19 (7.79)
Q_3 (L/h/kg)	0.99 (10.06)	1.50 (18.24)	0.63 (10.79)	1.59 (14.44)
V_3 (L/kg)	10.86 (10.65)	1.31 (13.12)	8.31 (10.26)	1.46 (13.99)
k_{wlg} (h^{-1})	0.26 (8.59)	1.22 (9.03)	0.18 (8.31)	1.17 (7.24)
PC_{wlg}	24.45 (4.20)	1.14 (4.62)	26.33 (4.77)	1.13 (4.01)
k_{ulg} (h^{-1})	0.46 (8.36)	1.24 (10.64)	0.22 (8.75)	1.38 (10.82)
PC_{ulg}	27.07 (5.32)	1.22 (6.25)	20.51 (5.70)	1.22 (5.96)
k_{les} (h^{-1})	0.23 (7.16)	1.11 (6.19)	0.11 (13.50)	1.87 (11.85)
PC_{les}	31.07 (3.51)	1.06 (5.63)	15.68 (8.02)	1.24 (9.70)
k_{Mwlg} (h^{-1})	0.23 (11.56)	2.06 (7.95)	0.20 (15.62)	1.30 (11.29)
PC_{Mwlg}	133.40 (4.95)	1.15 (5.18)	89.51 (6.30)	1.15 (5.06)
k_{Mulg} (h^{-1})	0.37 (7.95)	1.16 (7.80)	0.23 (14.70)	1.37 (10.13)
PC_{Mulg}	161.80 (4.89)	1.16 (4.23)	80.42 (6.40)	1.14 (5.51)
k_{Mles} (h^{-1})	0.20 (7.05)	1.12 (6.40)	0.12 (16.01)	1.75 (15.24)
PC_{Mles}	144.70 (4.13)	1.09 (4.22)	63.41 (15.73)	1.66 (14.26)

Supplemental Table 2. Summary statistics of compartmental model parameter distributions for BDQ and M2 in BALB/c and C3HeB/FeJ mice. Population geometric mean (GM) and population geometric standard deviation (GSD) of each parameter calculated from the corresponding posterior marginal distributions. Uncertainty of estimate provided as percent relative standard deviation (% RSD) calculated from 10,000 MCMC samples.