

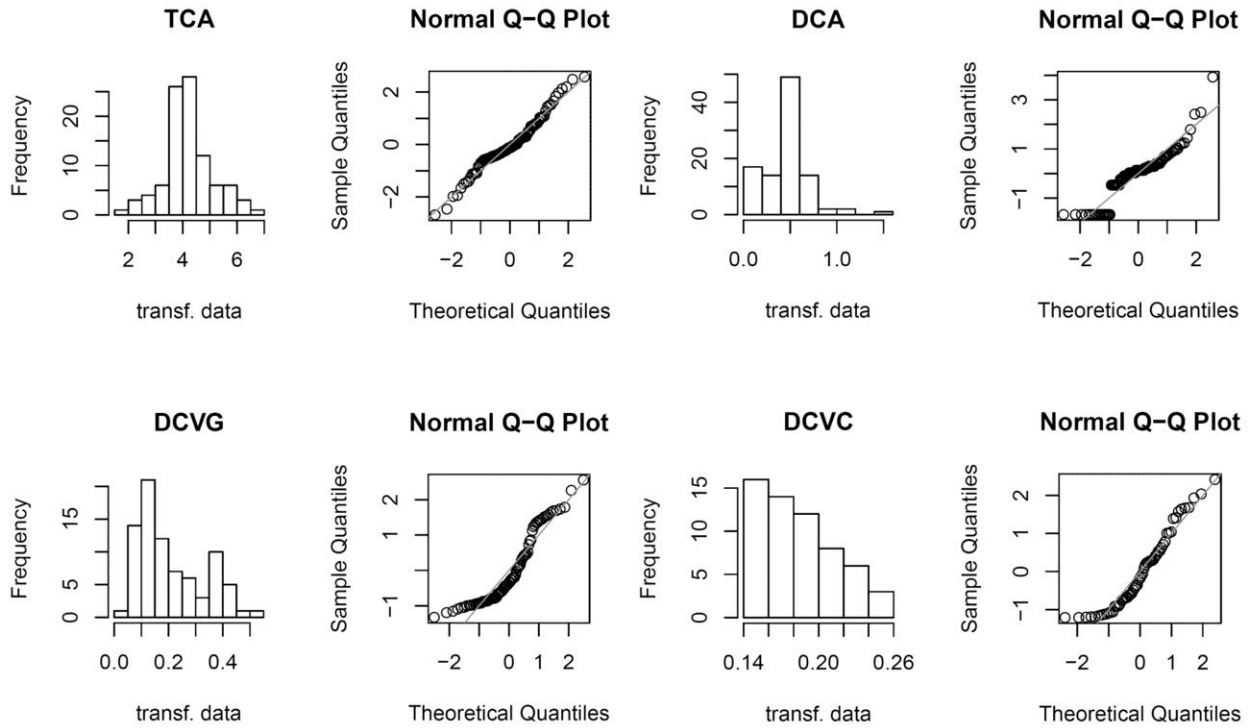
**Physiologically-Based Pharmacokinetic (PBPK) Modeling of Inter-strain  
Variability in Trichloroethylene Metabolism in the Mouse**

Weihsueh A. Chiu\*, Jerry L. Campbell Jr.<sup>†</sup>, Harvey J. Clewell 3rd<sup>†</sup>,  
Yi-Hui Zhou<sup>‡</sup>, Fred A. Wright<sup>‡</sup>, Kathryn Z. Guyton\*, and Ivan Rusyn<sup>§</sup>

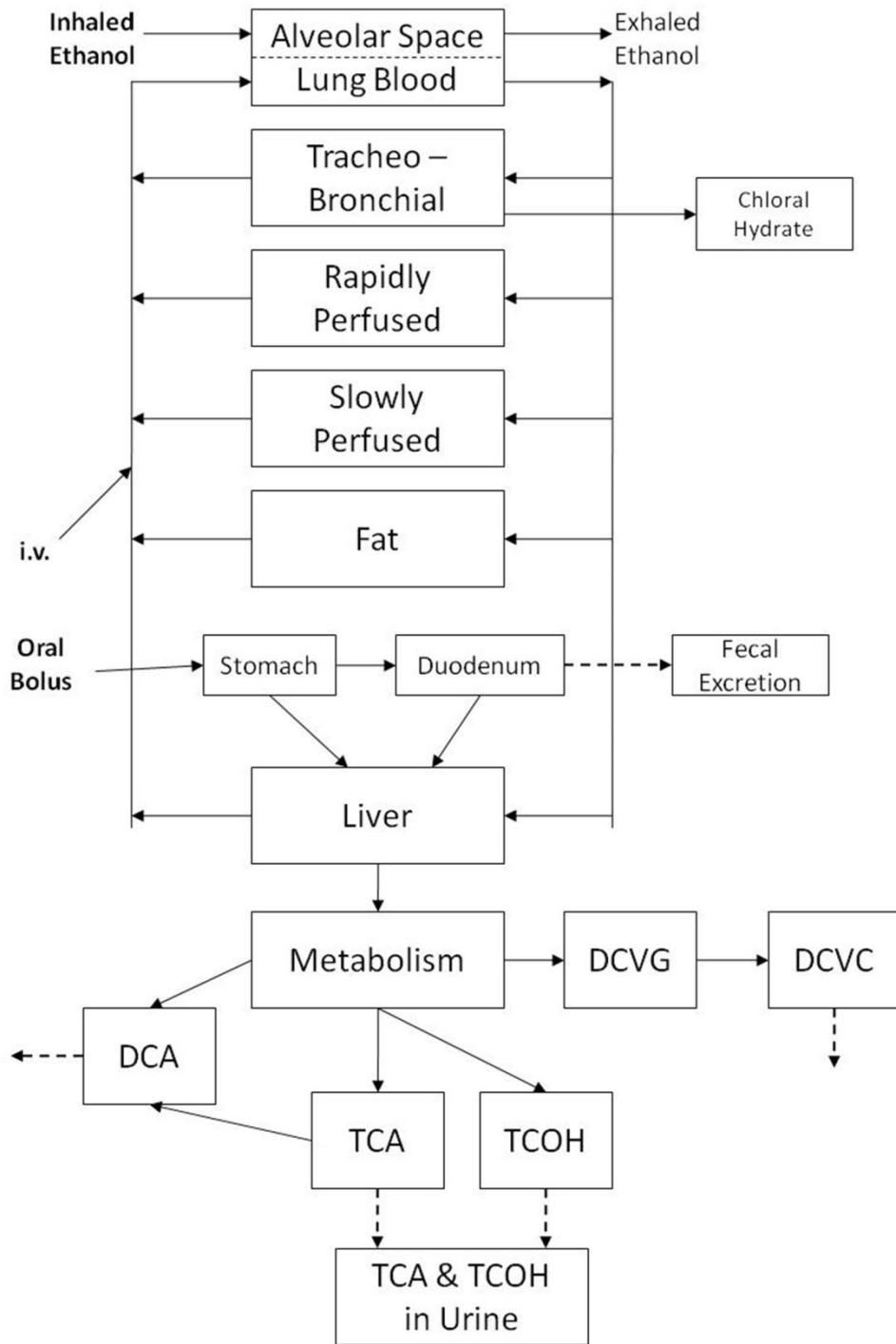
\*National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington DC, 20460; <sup>†</sup>The Hamner Institutes for Health Sciences, Research Triangle Park, NC 27709; Departments of <sup>‡</sup>Biostatistics and <sup>§</sup>Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, NC 27599

**Supplemental Figures**

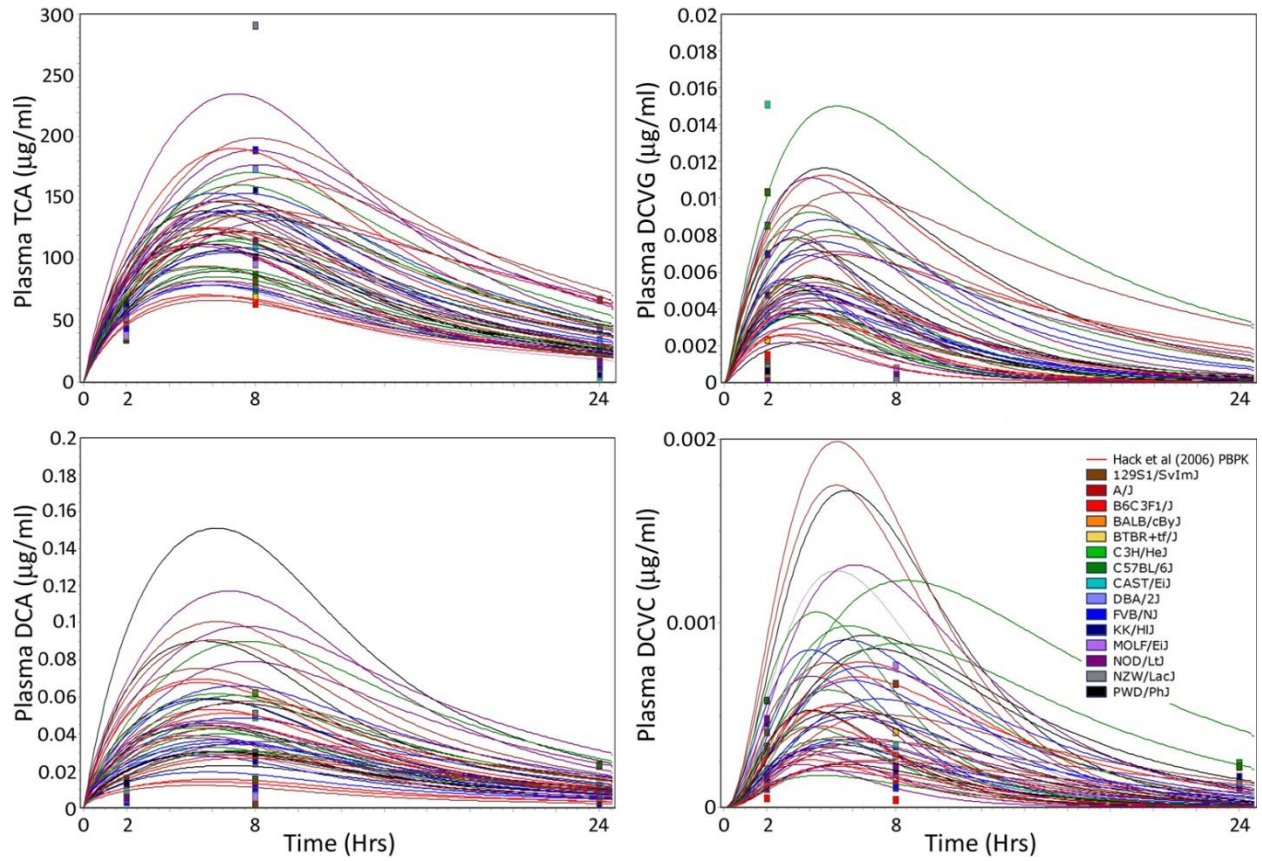
**Supplemental Figure 1.** Histograms of the transformed values and quantile-quantile plots for TCE metabolites TCA, DCA, DCVG and DCVC. The transformation  $y_{\text{new}}=y^{0.25}$  produced the closest average fit to normality across the metabolites, with no influential outliers.



**Supplemental Figure 2.** Schematic of the modified Hack et al. (2006) model.

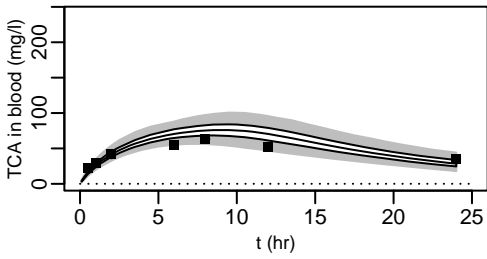


**Supplemental Figure 3.** Monte Carlo simulation (100 iterations) of the multi-strain mouse time-course data with the parameter distributions for metabolism and clearance of metabolites estimated to fit the range of measured values.

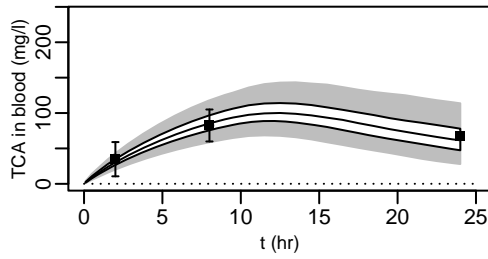


**Supplemental Figure 4.** Comparison of data (solid boxes with  $\pm 1$  SD error bars) and PBPK model predictions (solid lines: interquartile range; grey area: 95% confidence interval) for TCA in mouse inbred strains [data from (Bradford et al 2011)].

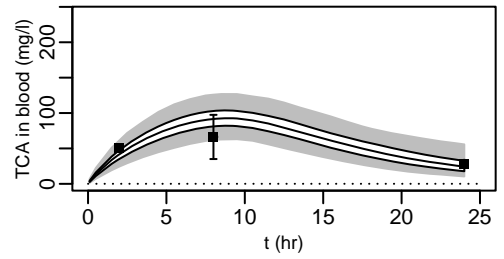
Kim et al. (2009) Male Mouse  
2140 mg/kg/d TCE corn oil gavage (single dose)



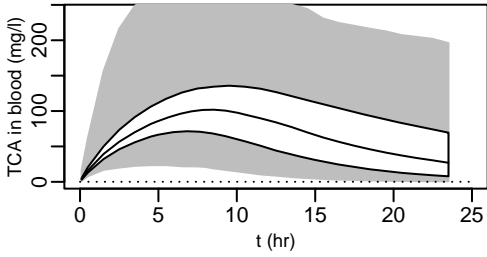
Bradford et al. (2011) 129S1/SvImJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



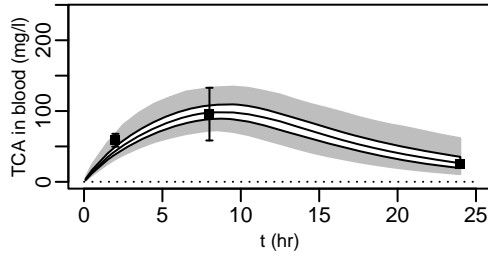
Bradford et al. (2011) A/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



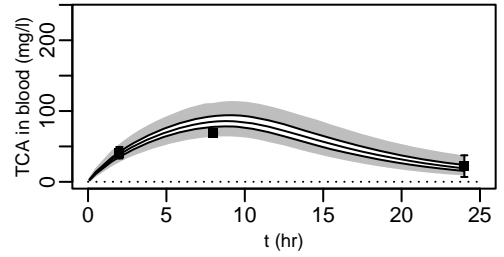
Bradford et al. (2011) AKR/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



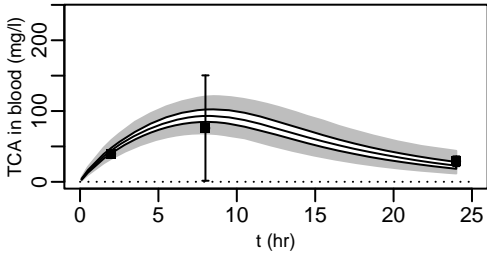
Bradford et al. (2011) BALB/cByJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



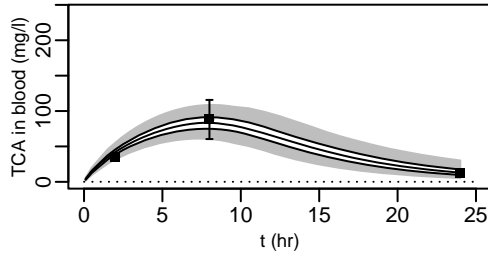
Bradford et al. (2011) BTBR+ tf/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



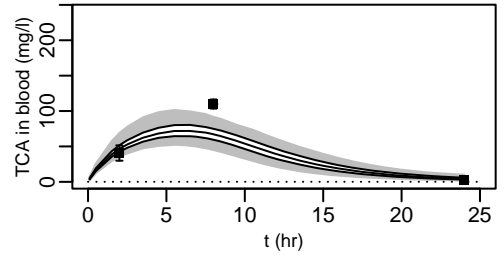
Bradford et al. (2011) C3H/HeJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



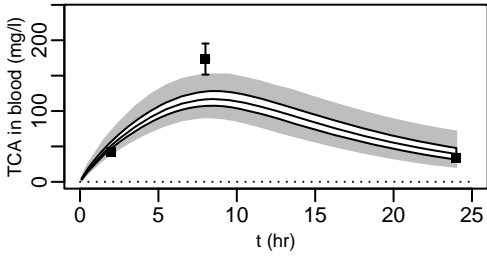
Bradford et al. (2011) C57BL/6J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



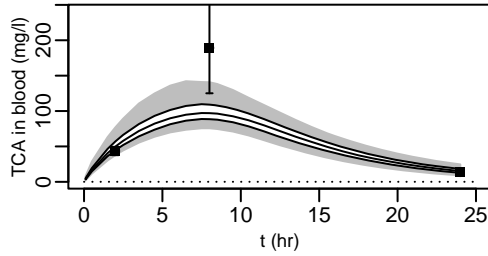
Bradford et al. (2011) CAST/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



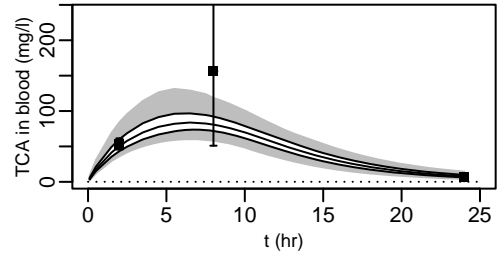
Bradford et al. (2011) DBA/2J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



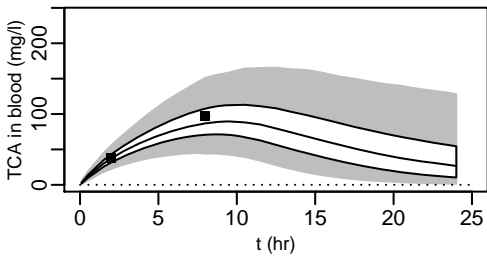
Bradford et al. (2011) FVB/NJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



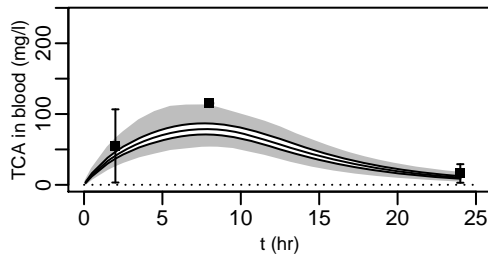
Bradford et al. (2011) KK/HIJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



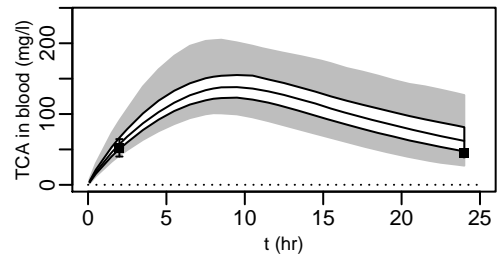
Bradford et al. (2011) MOLF/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



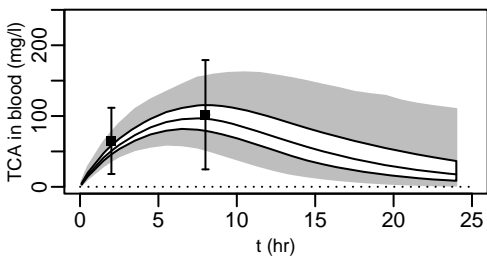
Bradford et al. (2011) NOD/LtJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



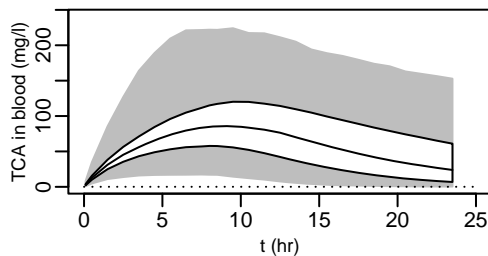
Bradford et al. (2011) NZW/LacJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) PWD/PhJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)

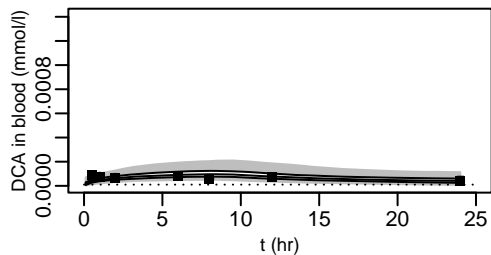


Bradford et al. (2011) WSB/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)

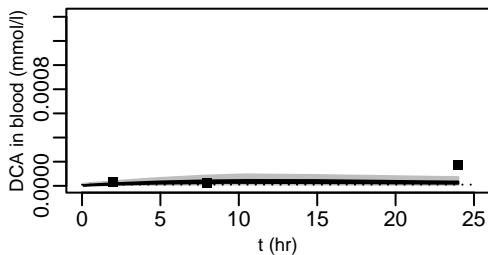


**Supplemental Figure 5.** Comparison of data (solid boxes with  $\pm 1$  SD error bars) and PBPK model predictions (solid lines: interquartile range; grey area: 95% confidence interval) for DCA in mouse inbred strains [data from (Bradford et al 2011)].

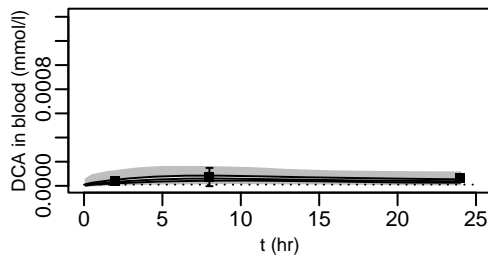
Kim et al. (2009) Male Mouse  
2140 mg/kg/d TCE corn oil gavage (single dose)



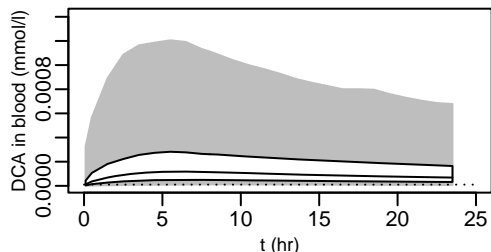
Bradford et al. (2011) 129S1/SvImJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



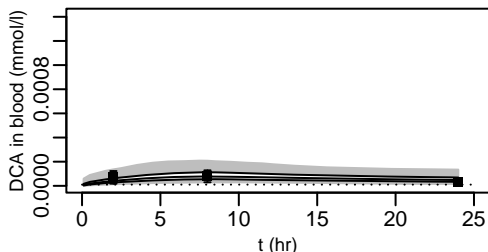
Bradford et al. (2011) A/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



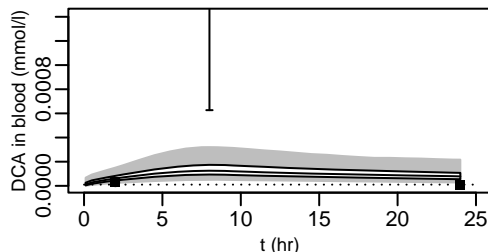
Bradford et al. (2011) AKR/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



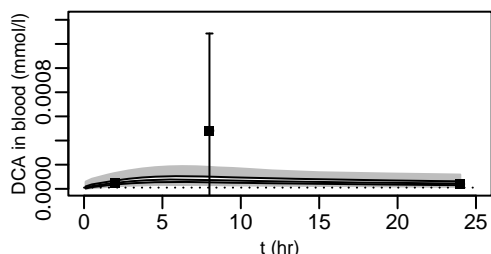
Bradford et al. (2011) BALB/cByJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



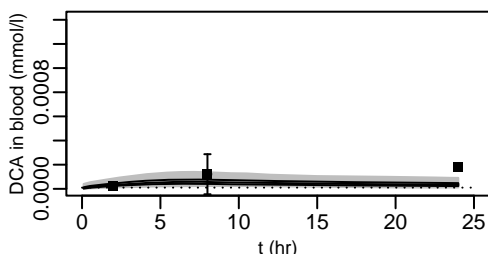
Bradford et al. (2011) BTBR+ tf/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



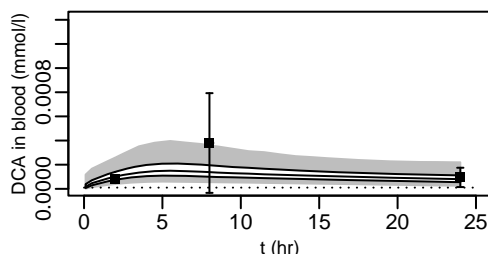
Bradford et al. (2011) C3H/HeJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



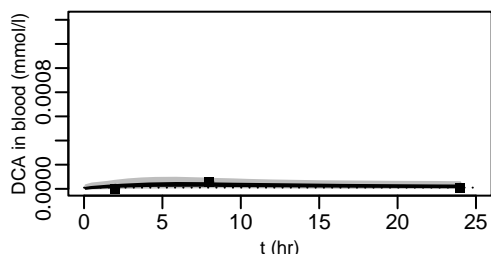
Bradford et al. (2011) C57BL/6J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



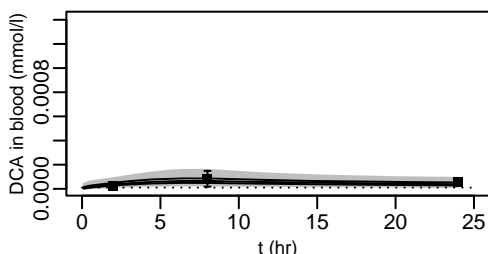
Bradford et al. (2011) CAST/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



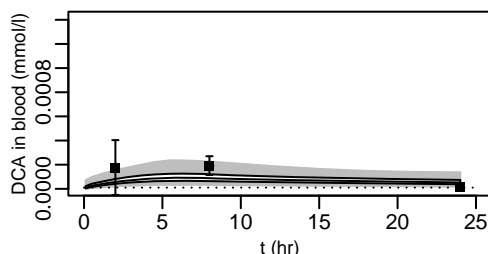
Bradford et al. (2011) DBA/2J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



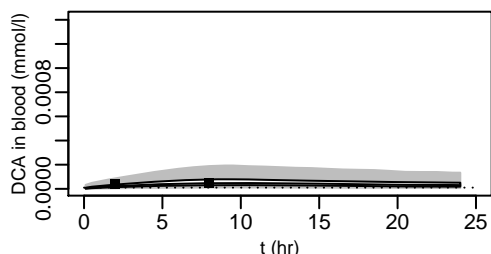
Bradford et al. (2011) FVB/NJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



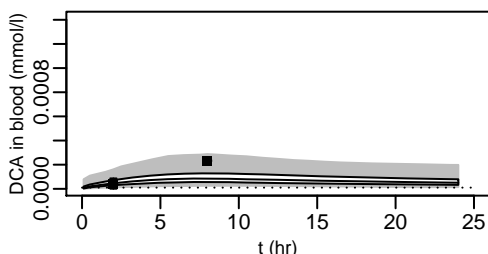
Bradford et al. (2011) KK/HIJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



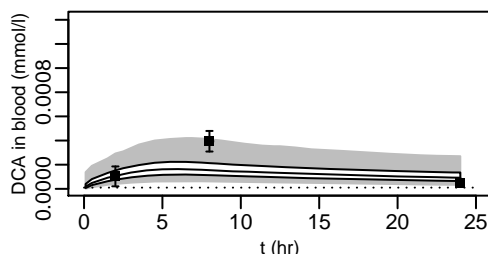
Bradford et al. (2011) MOLF/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



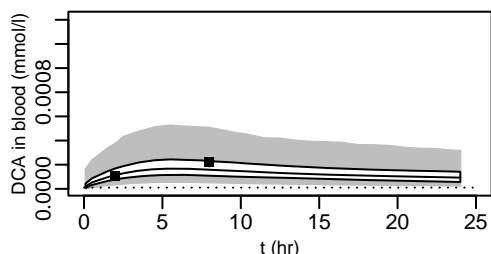
Bradford et al. (2011) NOD/LtJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



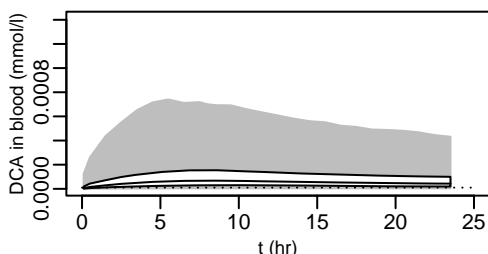
Bradford et al. (2011) NZW/LacJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) PWD/PhJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



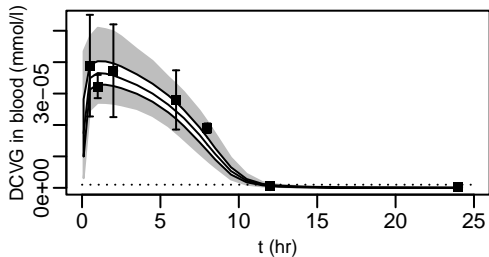
Bradford et al. (2011) WSB/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



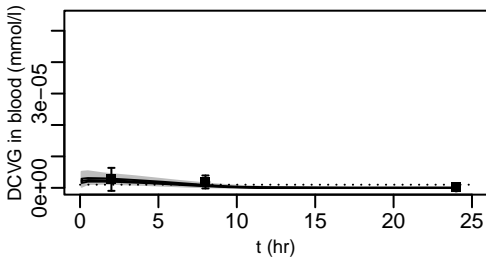


**Supplemental Figure 6.** Comparison of data (solid boxes with  $\pm 1$  SD error bars) and PBPK model predictions (solid lines: interquartile range; grey area: 95% confidence interval) for DCVG in mouse inbred strains [data from (Bradford et al 2011)].

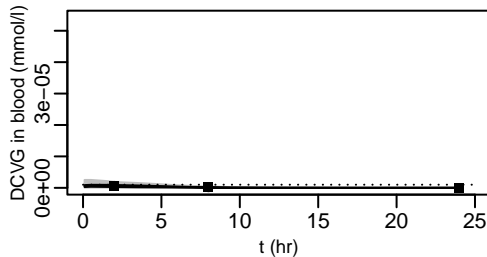
Kim et al. (2009) Male Mouse  
2140 mg/kg/d TCE corn oil gavage (single dose)



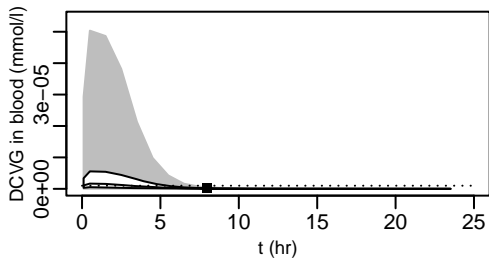
Bradford et al. (2011) 129S1/SvImJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



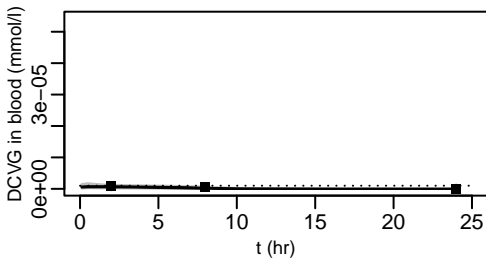
Bradford et al. (2011) A/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



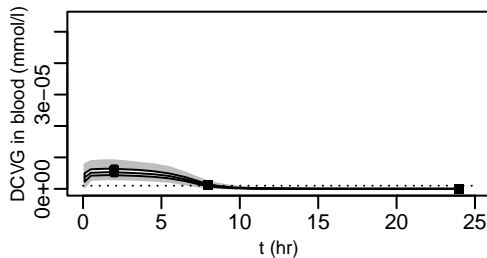
Bradford et al. (2011) AKR/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



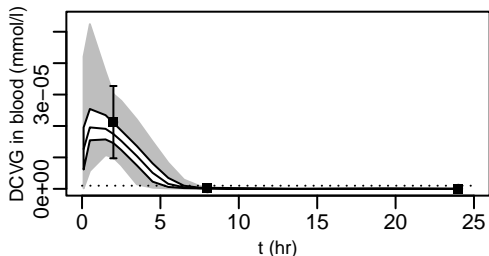
Bradford et al. (2011) BALB/cByJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



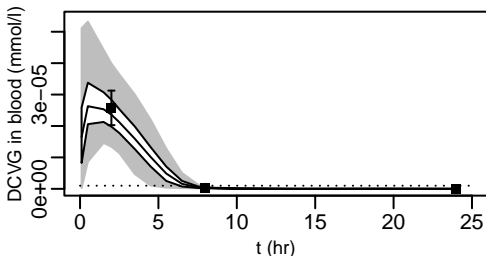
Bradford et al. (2011) BTBR+ tf/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



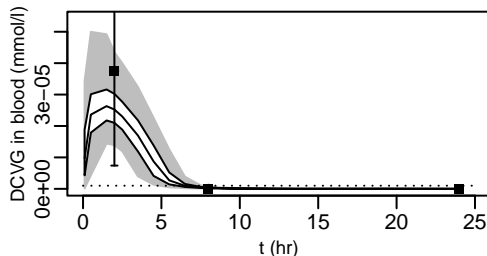
Bradford et al. (2011) C3H/HeJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



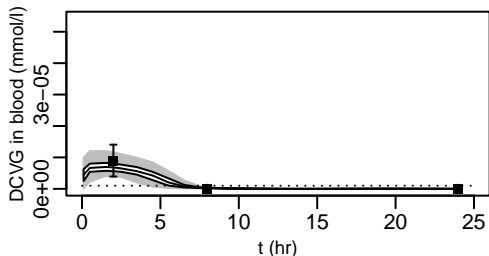
Bradford et al. (2011) C57BL/6J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



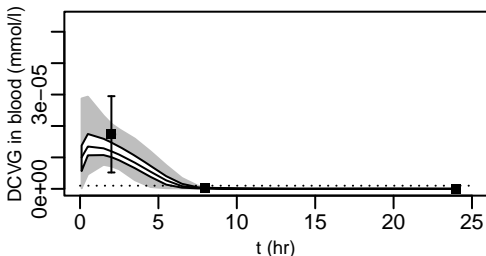
Bradford et al. (2011) CAST/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



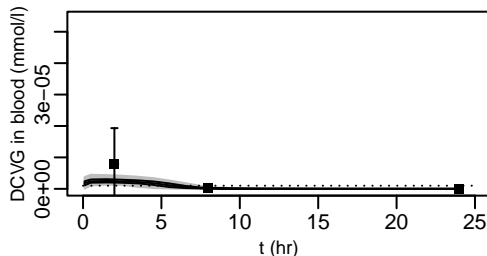
Bradford et al. (2011) DBA/2J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



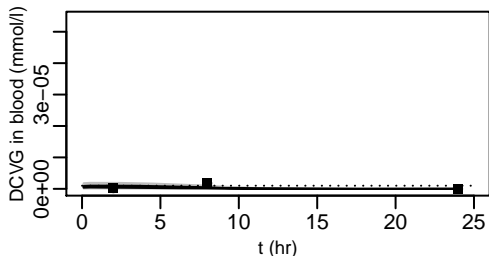
Bradford et al. (2011) FVB/NJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



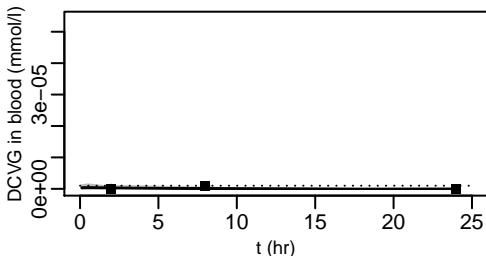
Bradford et al. (2011) KK/HlJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



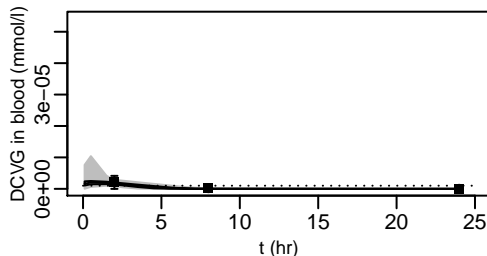
Bradford et al. (2011) MOLF/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



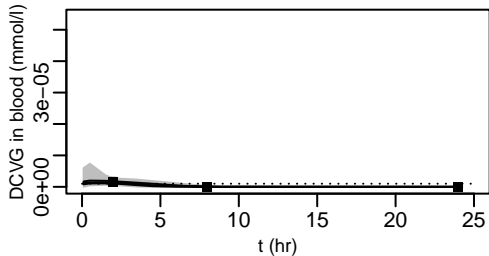
Bradford et al. (2011) NOD/LtJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



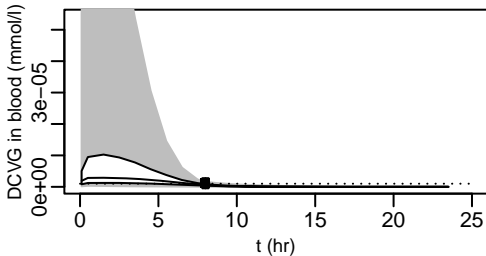
Bradford et al. (2011) NZW/LacJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) PWD/PhJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)

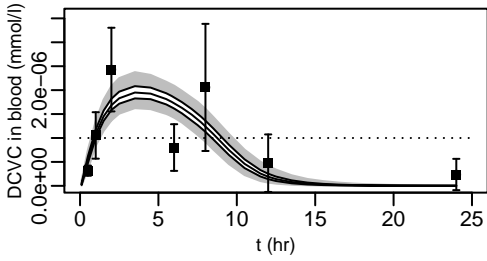


Bradford et al. (2011) WSB/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)

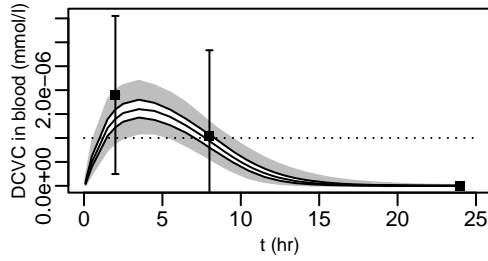


**Supplemental Figure 7.** Comparison of data (solid boxes with  $\pm 1$  SD error bars) and PBPK model predictions (solid lines: interquartile range; grey area: 95% confidence interval) for DCVC in mouse inbred strains [data from (Bradford et al 2011)].

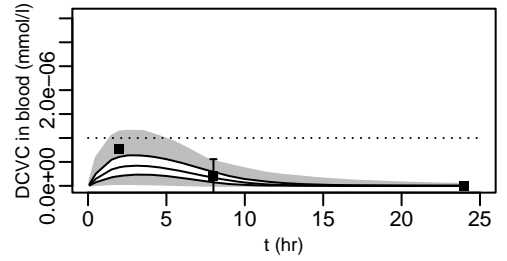
Kim et al. (2009) Male Mouse  
2140 mg/kg/d TCE corn oil gavage (single dose)



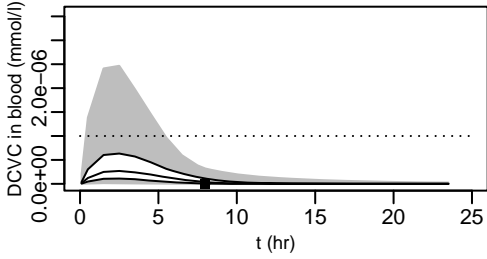
Bradford et al. (2011) 129S1/SvImJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



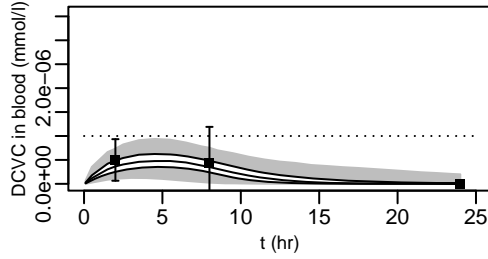
Bradford et al. (2011) A/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



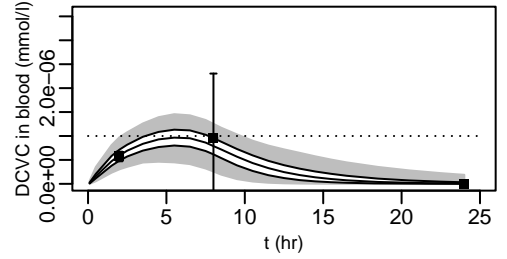
Bradford et al. (2011) AKR/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



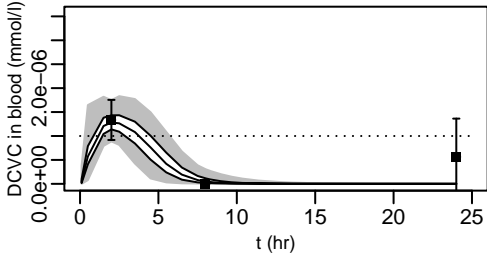
Bradford et al. (2011) BALB/cByJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



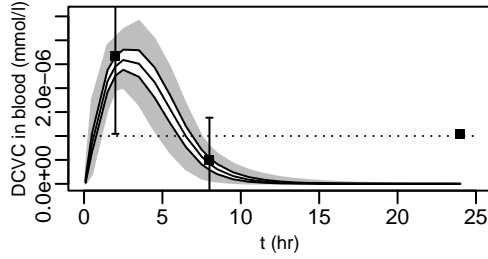
Bradford et al. (2011) BTBR+ tf/J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



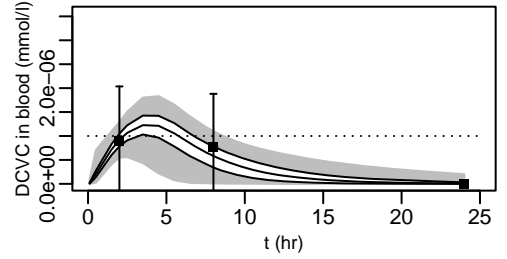
Bradford et al. (2011) C3H/HeJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



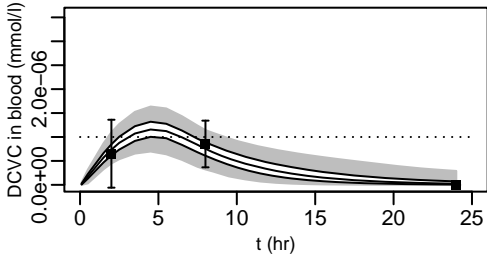
Bradford et al. (2011) C57BL/6J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



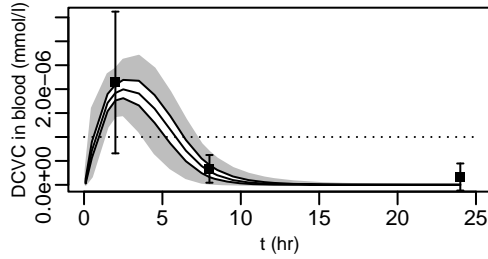
Bradford et al. (2011) CAST/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



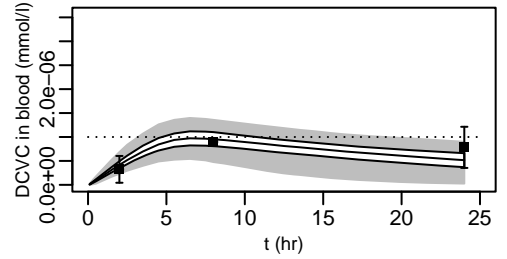
Bradford et al. (2011) DBA/2J Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



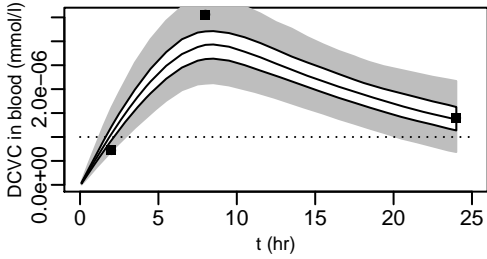
Bradford et al. (2011) FVB/NJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



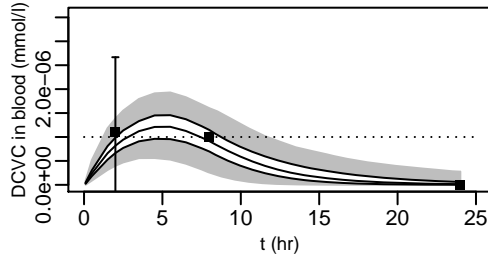
Bradford et al. (2011) KK/HIJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



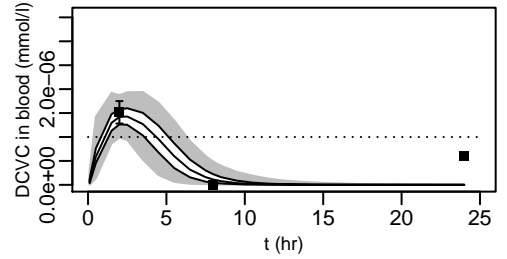
Bradford et al. (2011) MOLF/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



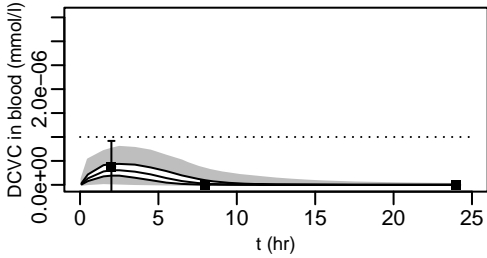
Bradford et al. (2011) NOD/LtJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) NZW/LacJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) PWD/PhJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)



Bradford et al. (2011) WSB/EiJ Male Mouse  
2100 mg/kg/d TCE corn oil gavage (single dose)

