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Supplemental Material

Using Collaborative Cross Mouse Population to Fill Data Gaps in Risk Assessment: A Case Study of Population-Based Analysis of Toxicokinetics and Kidney Toxicodynamics of Tetrachloroethylene

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Figure S1. Toxicokinetic parameters of TCVG in serum (A) and liver (B) of PERC-treated mice. Shown are concentration-time profiles (A-B) and the area under the curve ($AUC_{0\text{-}12}$, C-D) for TCVG in mouse serum and liver after oral dosing with PERC (1000 mg/kg, single dose). A two-phase exponential association was used to fit the concentration-time profiles of TCVG, exemplified by representative lines in strains CC075 (blue), CC001 (green), CC023 (red), CC037 (maroon), and CC021 (brown). Black line indicates the population estimate based on 45 strains. Dark grey shaded area shows the 95% confidence interval of the population estimate, and light grey shaded area highlights the 95% prediction interval of the fitted curve. Area under the curve for each strain was calculated from 0 to 12 hours after dosing by using the trapezoidal rule.

Figure S2. Toxicokinetic parameters of TCVC in serum (A) and liver (B) of PERC-treated mice. Shown are concentration-time profiles (A-B) and the area under the curve ($AUC_{0\text{-}12}$, C-D) for TCVC in mouse serum and liver after oral dosing with PERC (1000 mg/kg, single dose). A two-phase exponential association was used to fit the concentration-time profiles of TCVC, exemplified by representative lines in strains CC075 (blue), CC001 (green), CC023 (red), CC037 (maroon), and CC021 (brown). Black line indicates the population estimate based on 45 strains. Dark grey shaded area shows the 95% confidence interval of the population estimate, and light grey shaded area highlights the 95% prediction interval of the fitted curve. Area under the curve for each strain was calculated from 0 to 12 hours after dosing by using the trapezoidal rule.

Figure S3. Toxicokinetic parameters of NAcTCVC in serum (A) and liver (B) of PERC-treated mice. Shown are concentration-time profiles (A-B) and the area under the curve (AUC_{0-12}, C-D) for NAcTCVC in mouse serum and liver after oral dosing with PERC (1000 mg/kg, single dose). A two-phase exponential association was used to fit the concentration-time profiles of NAcTCVC, exemplified by representative lines in strains CC075 (blue), CC001 (green), CC023 (red), CC037 (maroon), and CC021 (brown). Black line indicates the population estimate based on 45 strains. Dark grey shaded area shows the 95% confidence interval of the population estimate, and light grey shaded area highlights the 95% prediction interval of the fitted curve. Area under the curve for each strain was calculated from 0 to 12 hours after dosing by using the trapezoidal rule.

Figure S4. Correlation analysis of the phenotypes collected in this study. Pairwise correlations between tissue-specific AUCs and toxicodynamic phenotypes were calculated by using Pearson's method. The diagonal (top left to bottom right) shows the frequency distribution of data points for each phenotype. The bottom-left section of the chart shows X-Y scatter plots for each two phenotypes. The top-right section of the chart shows Pearson's correlation values for each two phenotypes, as well as statistical significance level based on F-test (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ● $p < 0.1$). Abbreviations: NAc=NAcTCVC; BW=body weight; TG=triglycerides.

Figure S5. Effects of PERC (1000 mg/kg, single dose) on kidney weights (A and B) and kidney to body weight ratios (C and D) in Collaborative Cross mice. Dumbbell plots (A and C) illustrate the effects of PERC (red circles) in comparison to vehicle (black dots) in each strain. Scattered dot plots (B and D) show the population variability within each group. Grey line connects the effects within a single mouse strain. Significance was determined using Wilcoxon matched-pairs (i.e., strains) signed rank test.

Figure S6. Effects of PERC (1000 mg/kg, single dose) on kidney mRNA expression of PPARα responsive genes (*Acot 1, Fabp1*, and *Ehhadh*) in Collaborative Cross mice. Dumbbell plots illustrate the effects of PERC (red circles) in comparison to vehicle (black dots) in each Collaborative Cross strain.

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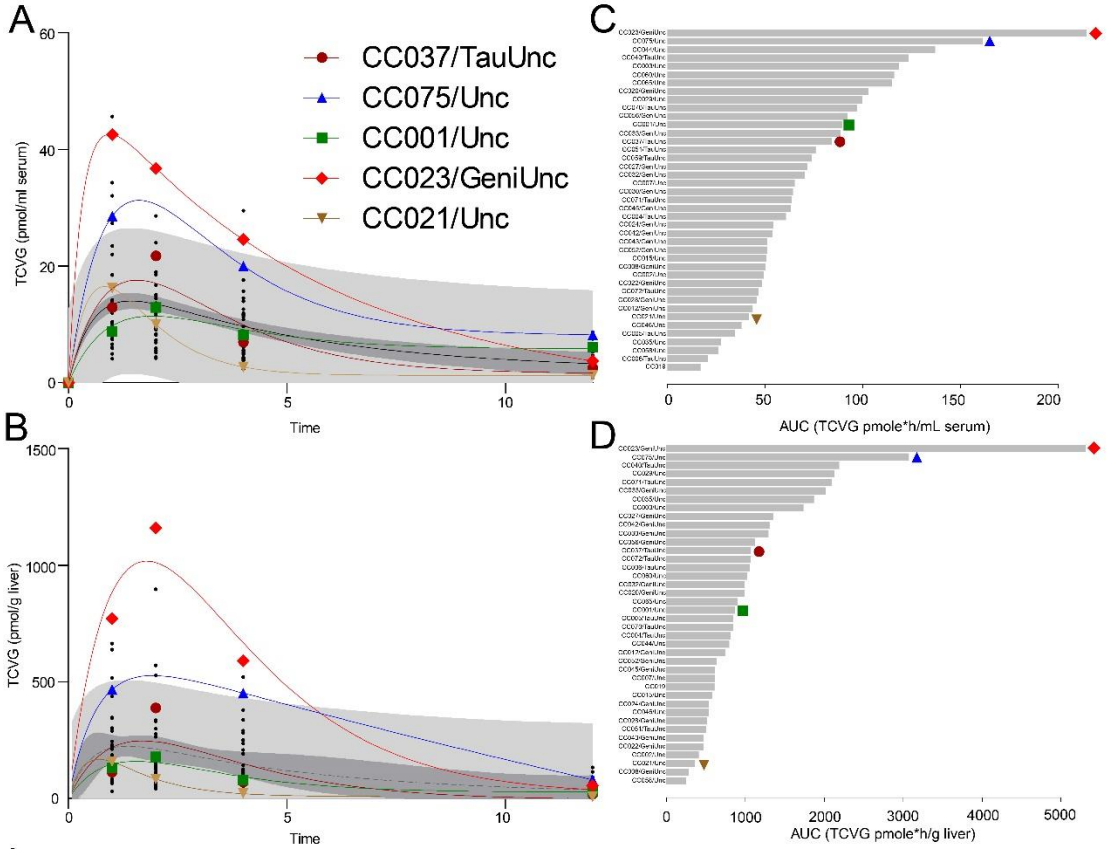

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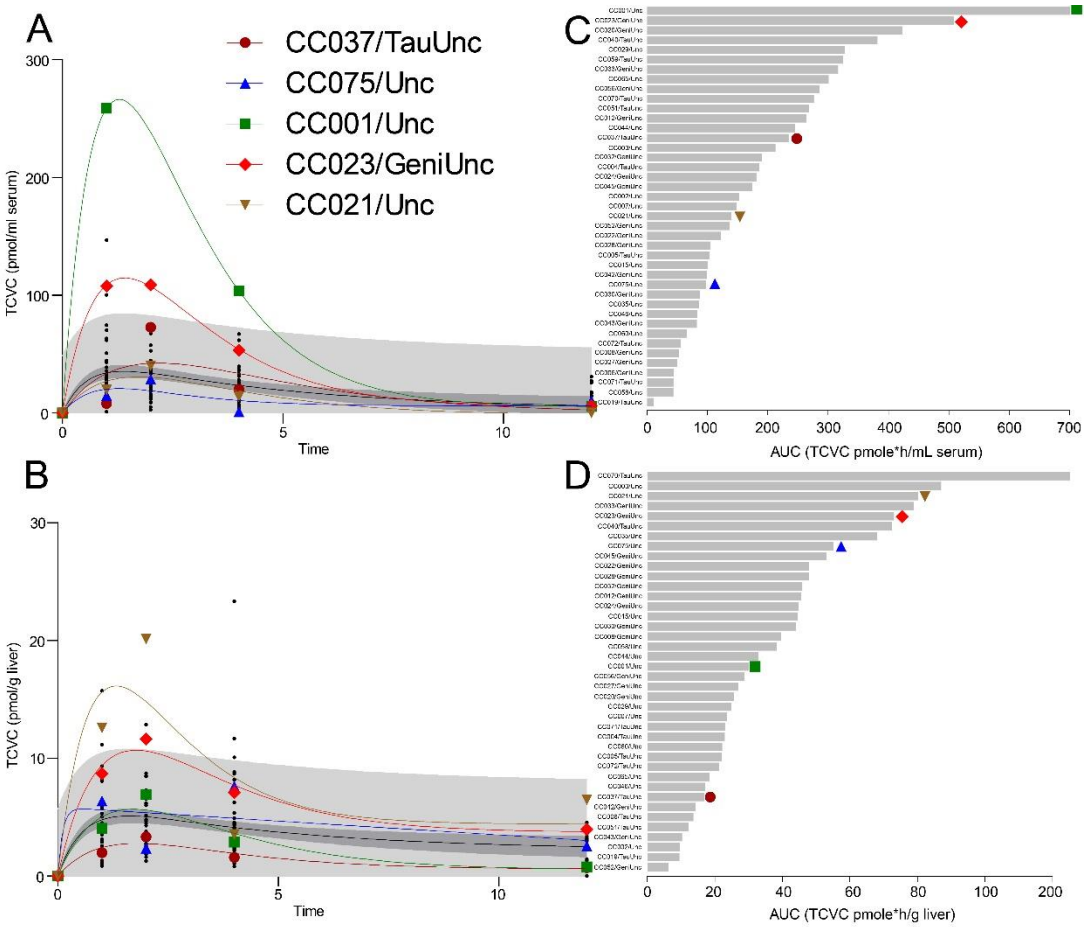

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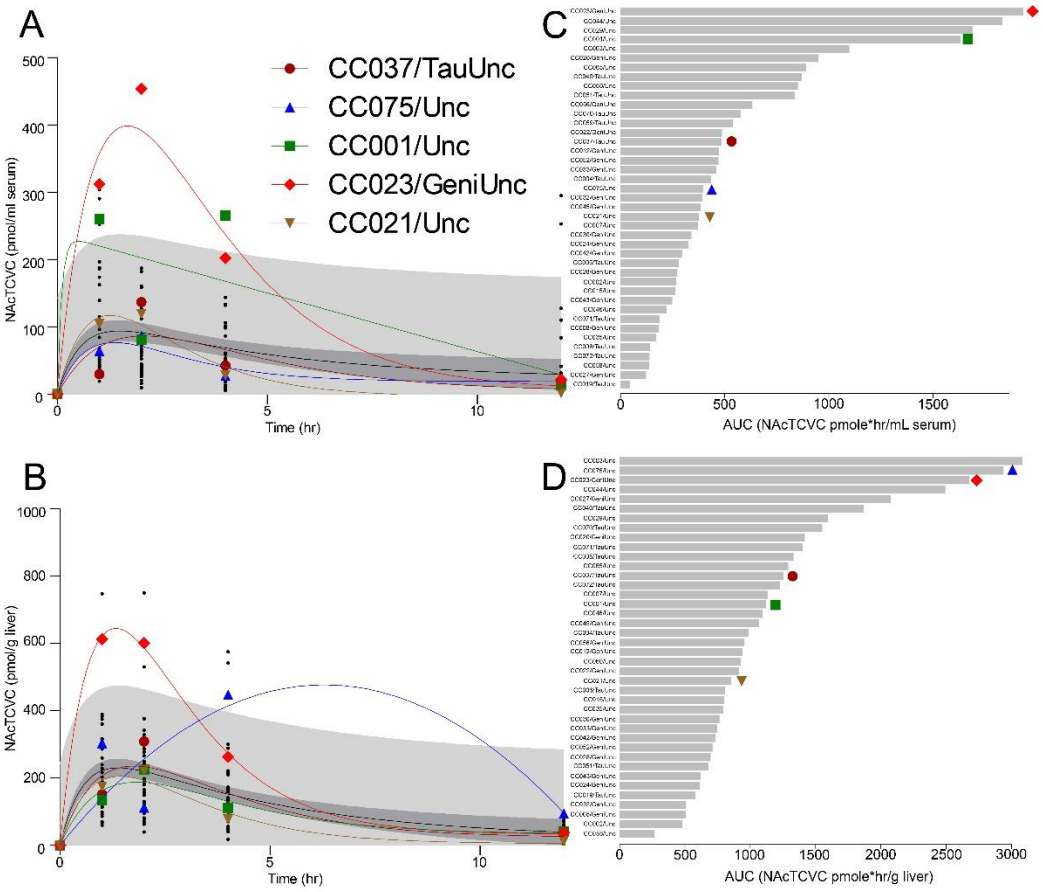

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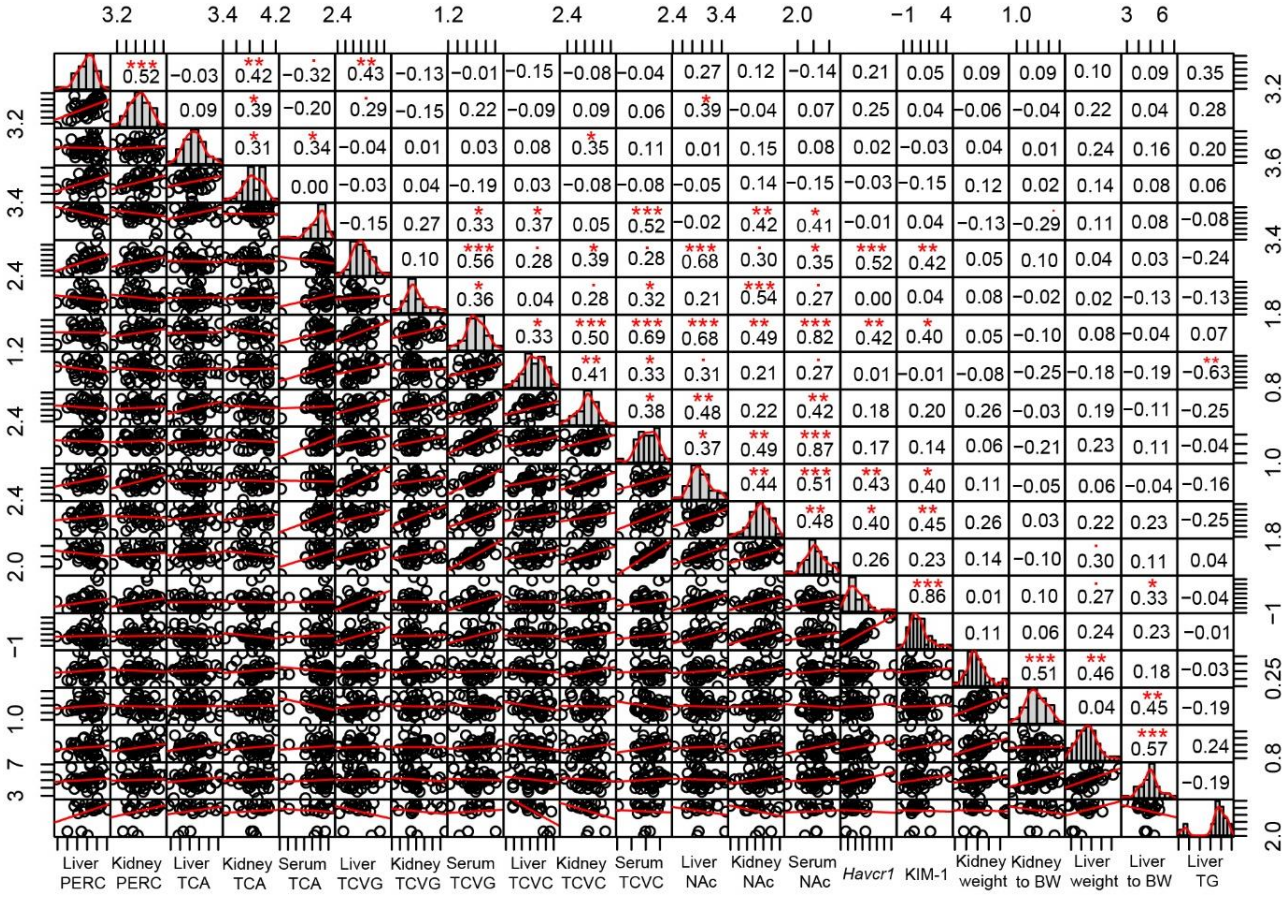

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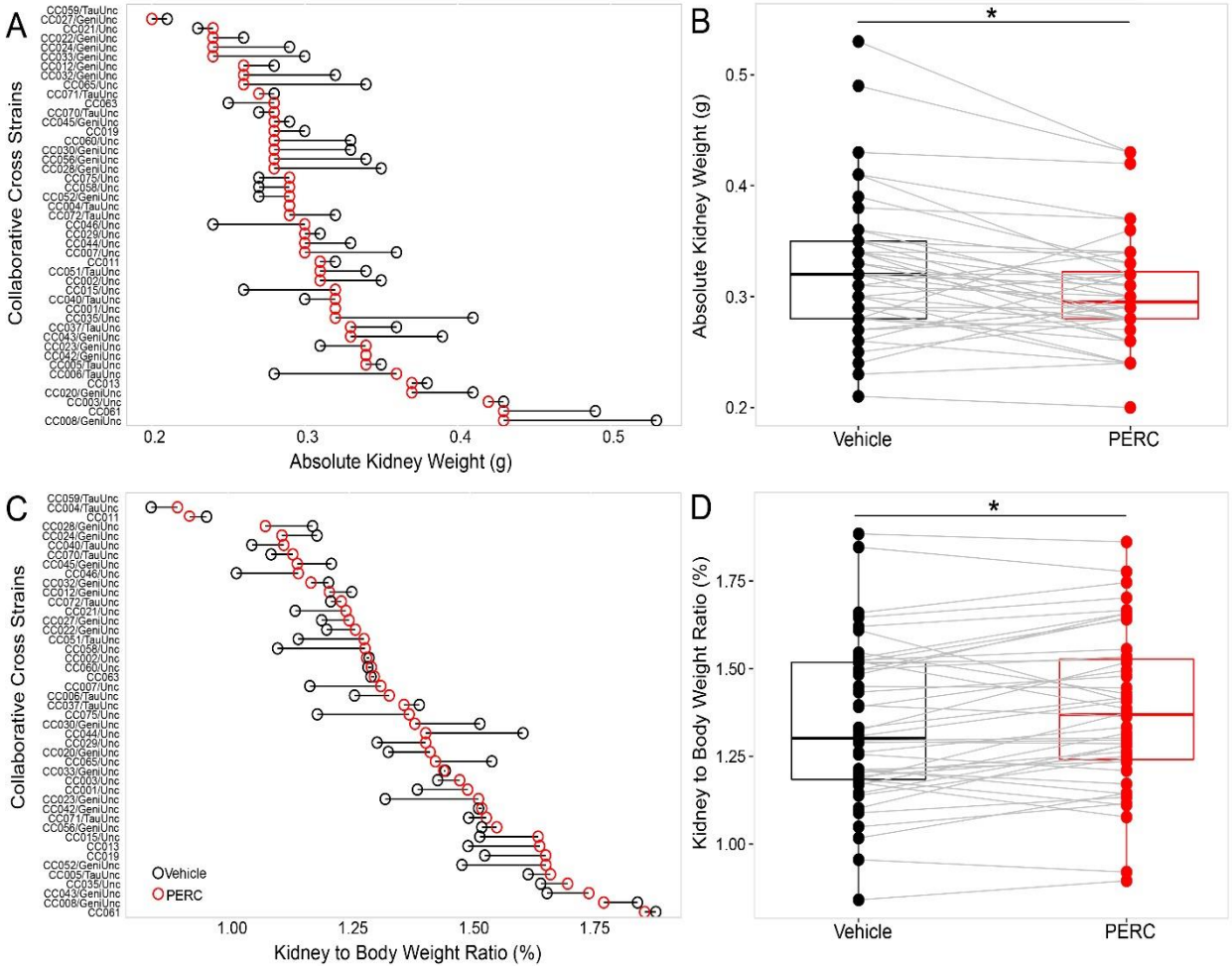

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