PBPK Modeling Update for Trichloroethylene (TCE) and Metabolites

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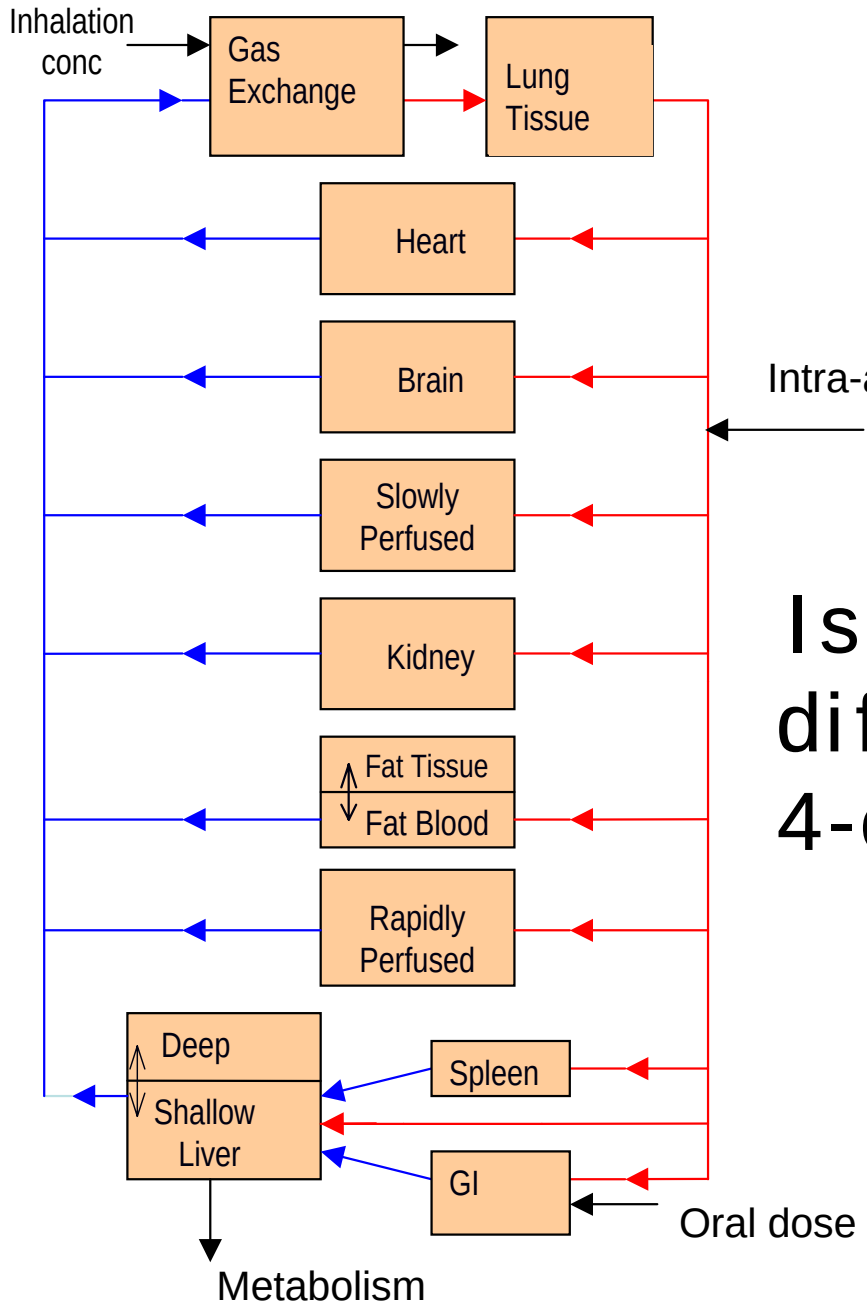
What is new since the TCE EHP 2000 Monograph?

- Rat TCE PBPK model
- Species specific binding of TCA in serum
- Mouse and rat PBPK model for DCA
- Harmonization of Clewell et al. and Fisher et al. PBPK models

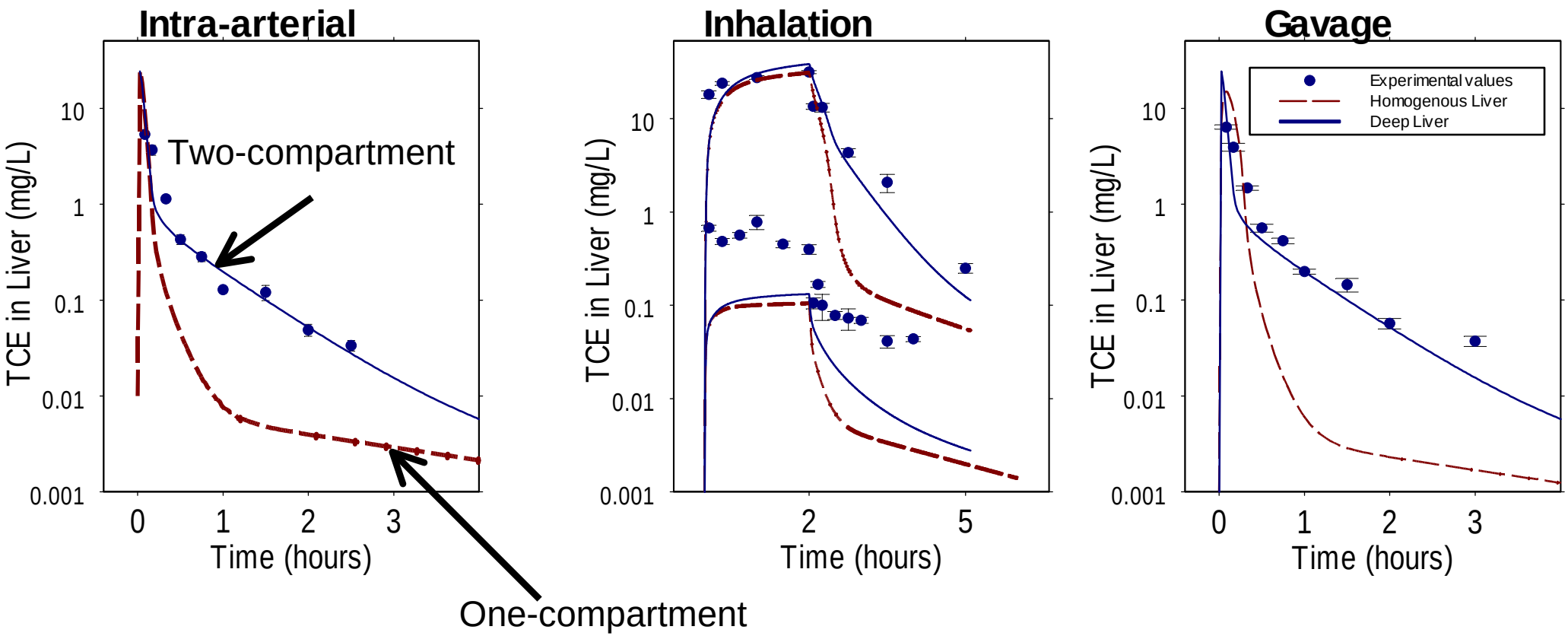
New TCE PBPK Model in the Rat



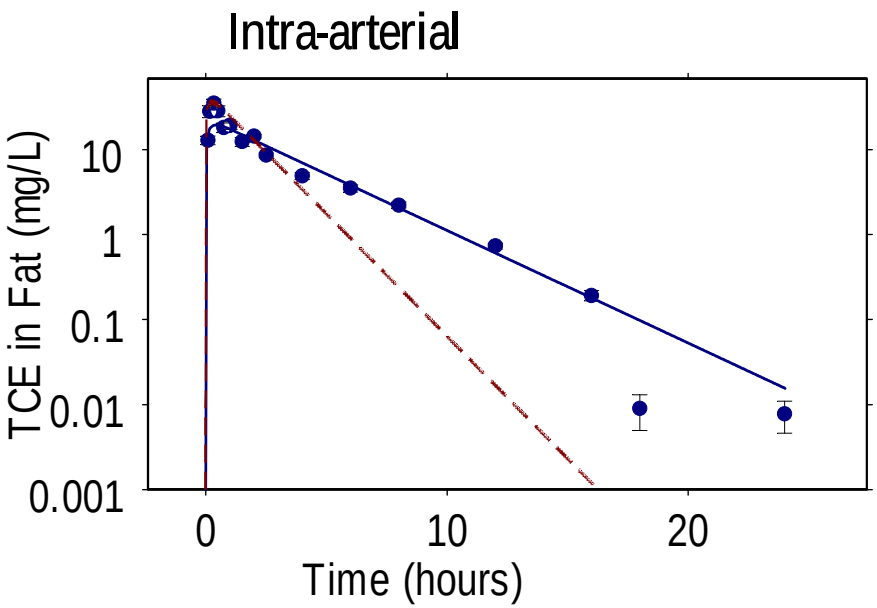
Keys, D. A., James V. Bruckner, Srinivasa Muralidhara and Jeffrey W. Fisher. 2003. Tissue Dosimetry Expansion and Cross-Validation of Rat and Mouse Physiologically Based Pharmacokinetic Models for Trichloroethylene. Toxicological Sciences, 76, 35-50

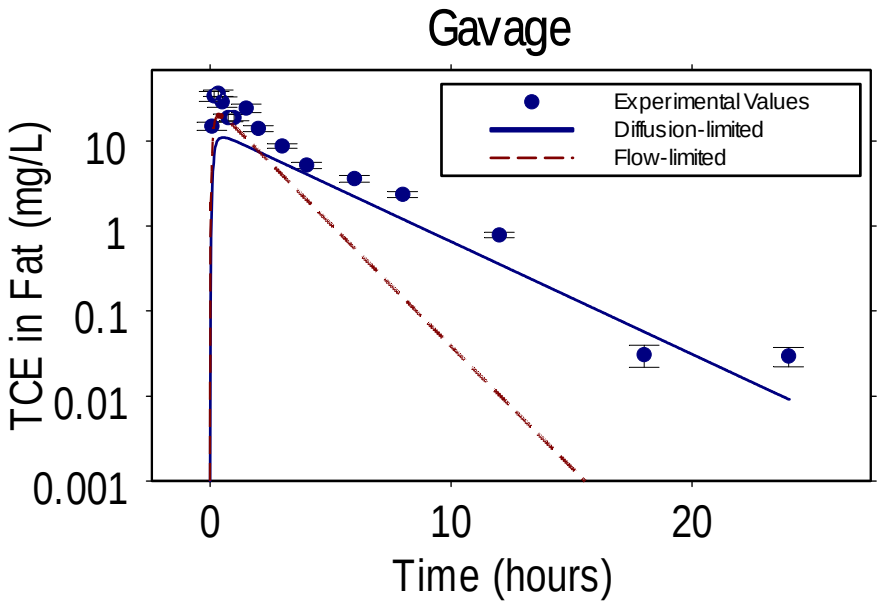
Is a 10-compartment model different than a 4-compartment model?

One compartment does not work as well as two compartments in liver.



Clearance from fat slower than predicted by flow-limited assumptions.





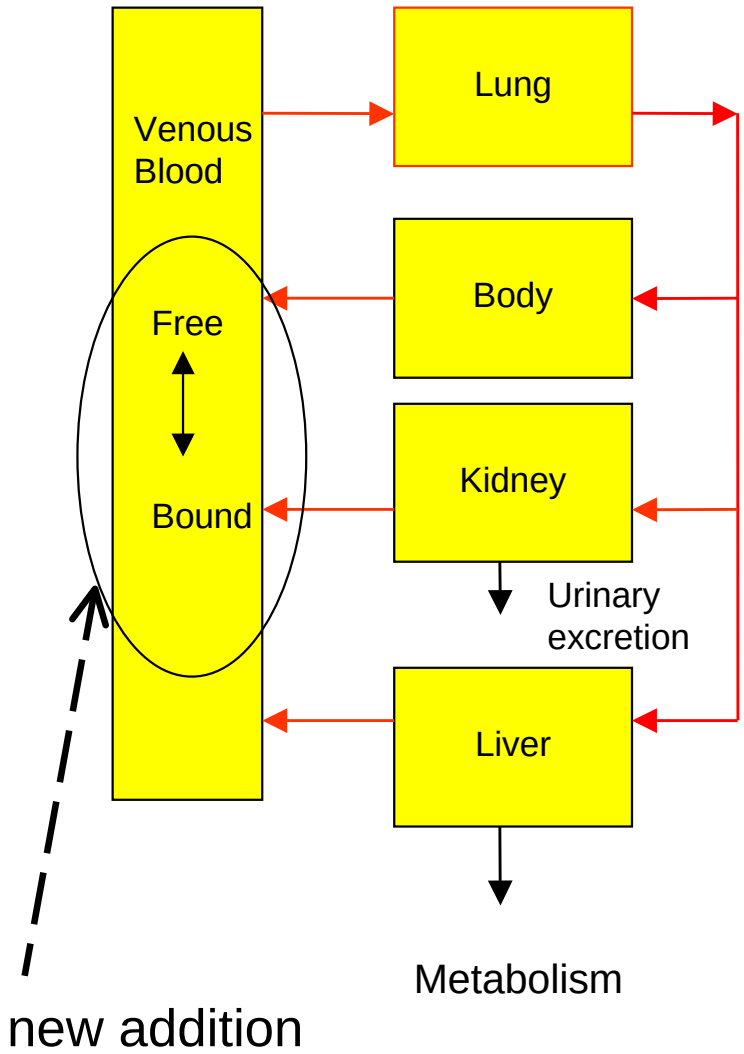
TCE PBPK Modeling Results

- 'Deep liver' captures slow hepatic clearance of TCE in rats and mice. Insensitive to metabolism in 'shallow liver'.

- Diffusion-limited fat describes slow fat clearance of TCE in the rat. Sensitive model parameter.

- For richly perfused organs, adding additional compartments is ok, if necessary, lumped compartment is fine.

New TCA sub-model for TCE PBPK model with blood protein binding (in progress).

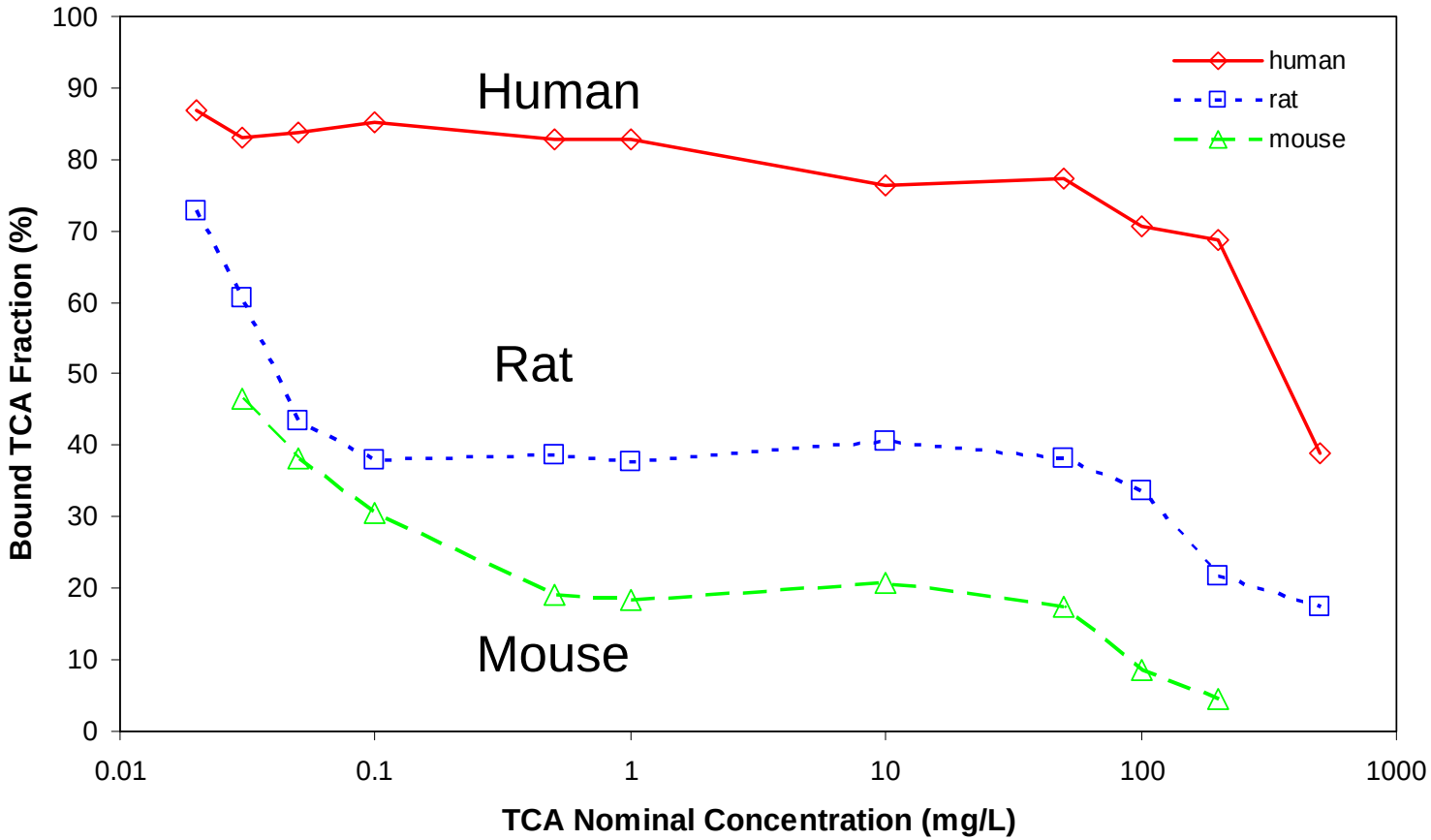


Abbas R and Fisher JW (1997) A physiologically based pharmacokinetic model for trichloroethylene and its metabolites, chloral hydrate, trichloroacetate, dichloroacetate, trichloroethanol, and trichloroethanol glucuronide in B6C3F1 mice. *Toxicol Appl Pharmacol* **127:** 15-30.

Fisher, J.W., Mahle, D., Abbas, R. (1998) A human physiologically based pharmacokinetic model for trichloroethylene and its metabolites trichloroacetic acid and free trichloroethanol. *Toxicol. Appl. Pharmacol.* **152**, 339-359

Serum binding studies with TCA to calculate the free and bound fractions of TCA by equilibrium dialysis in human, mice and rat serum.

Lumpkin, Michael H., James V. Bruckner, Jerry L. Campbell, Cham E. Dallas, Catherine A. White, and Jeffrey W. Fisher. 2003. Plasma Binding of Trichloroacetic Acid in Mice, Rats, and Humans under Cancer Bioassay and Environmental Exposure Conditions. Drug Metabolism and Disposition 31, 1203-1207.



Incorporation of Serum Binding into TCA PBPK Model

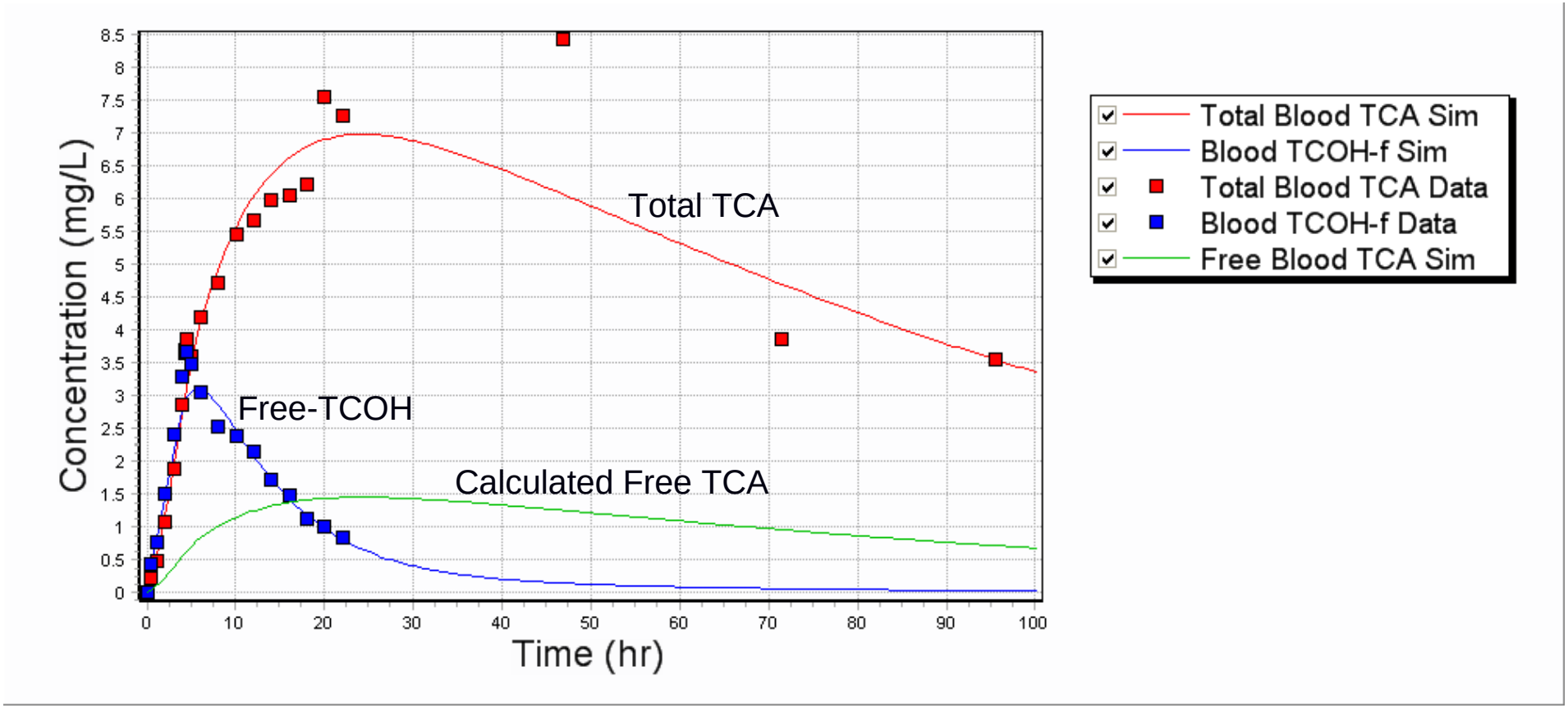
$$C_{free} = \frac{1}{2}\sqrt{(K_d + (N * P) - C_{total}) + 4 * K_d * C_{total}} - (K_d + (N * P) - C_{total})$$

P = plasma albumin concentration, N = number of binding sites/albumin molecule, Kd = equilibrium dissociation constant (fitted with WinNonlin)

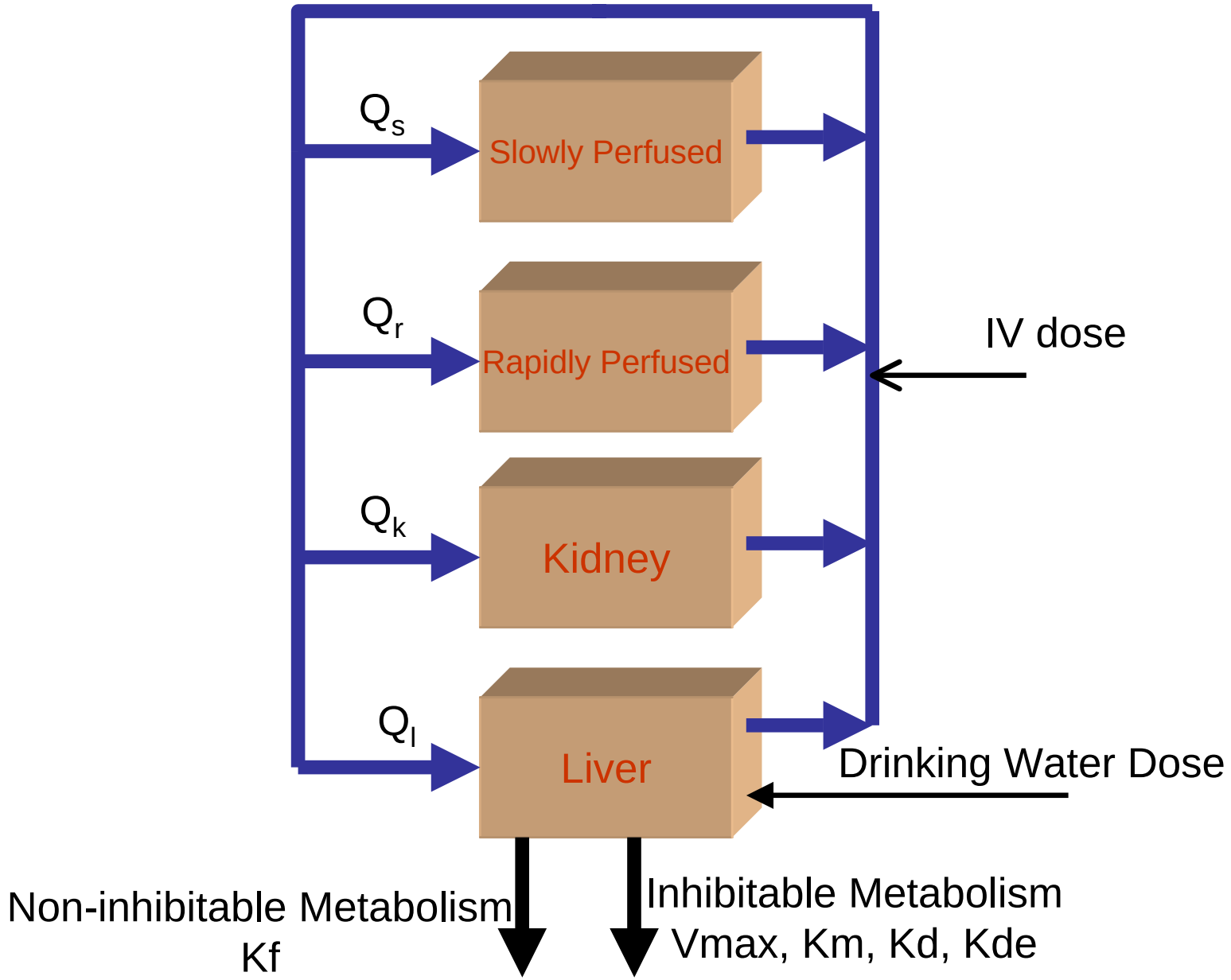
Frazier JM, Pelekis M, Toxopeus JH, and Foy B (1998) Determination of constants of water soluble chemicals for biologically based kinetic models. U.S. Air Force Research Laboratory. Technical Report AFRL-HE-WP-TR-1998-0113, Wright-Patterson Air Force Base, OH.

Human PBPK Model – Blood Time Courses

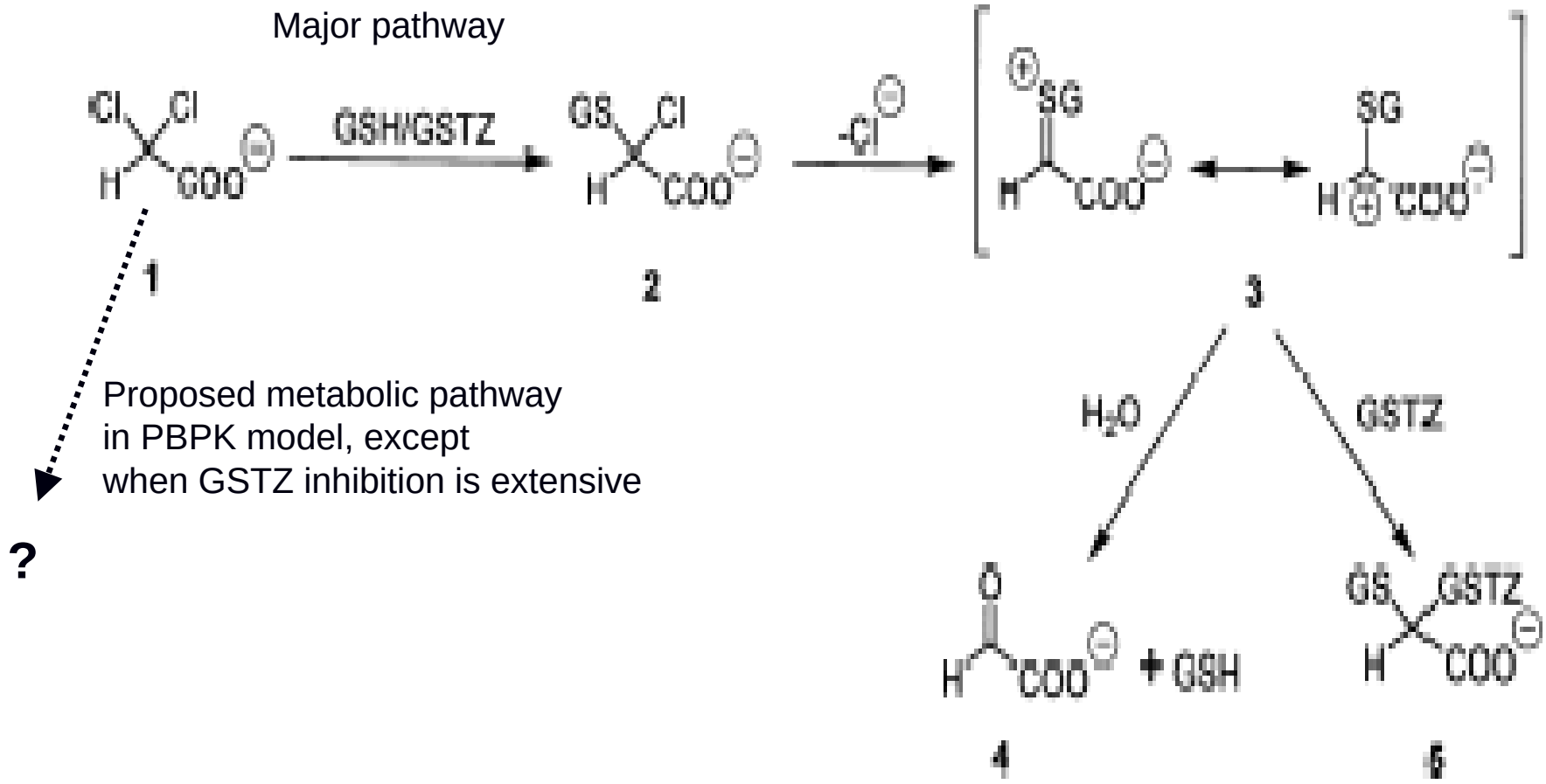
•Concentrations of TCA (•) and TCOH-f (•) in blood of male exposed to 100 ppm TCE for 4 h for the individual male subject.



DCA Rat & Mouse PBPK Model (in progress)



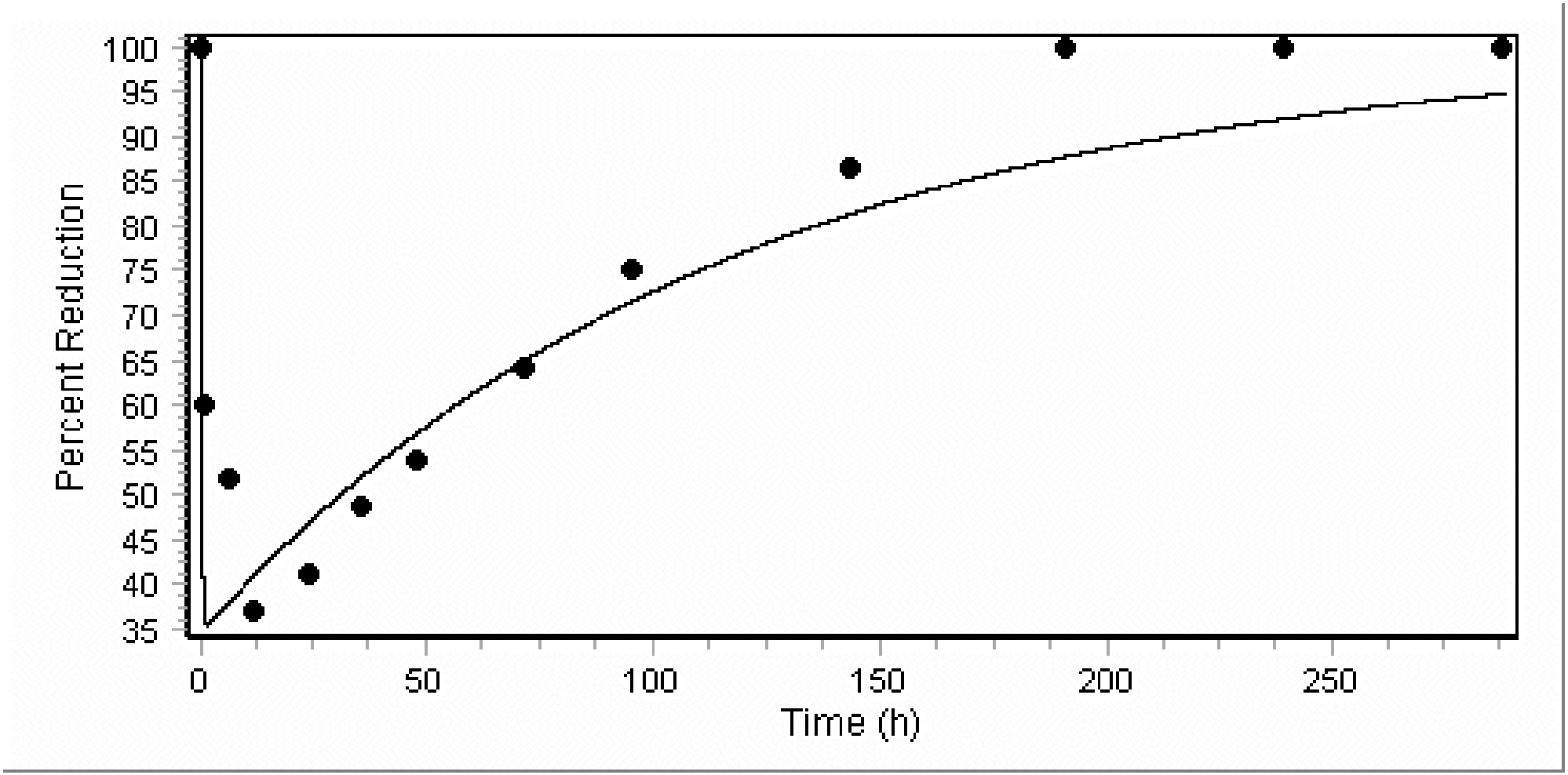
Proposed Mechanism for GSTZ Metabolism of DCA



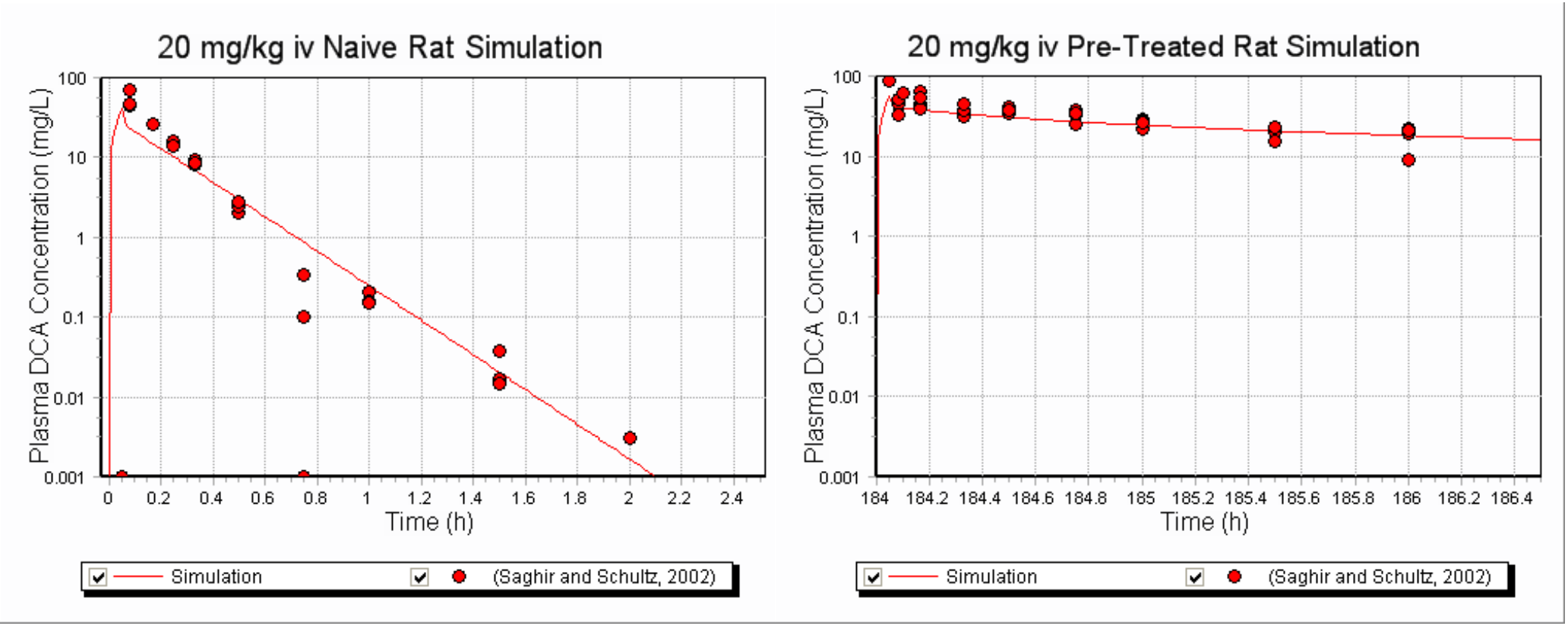
(Anders et al., 2001)

Model simulation of the percentage reduction of the time-dependent maximum rate of DCA metabolism, Vmax(t) and the measured immunoreactive GSTZ protein activity (•) following an ip infusion of 38.7 mg/kg DCA.

Anderson, WB; Board, PG; Gargano, B; et al. (1999) Inactivation of glutathione transferase Zeta by dichloroacetic acid and other fluorine-lacking "-haloalkanoic acids. Chem Res Toxicol 12,1144-1149.



Control vs. Pretreated Rats

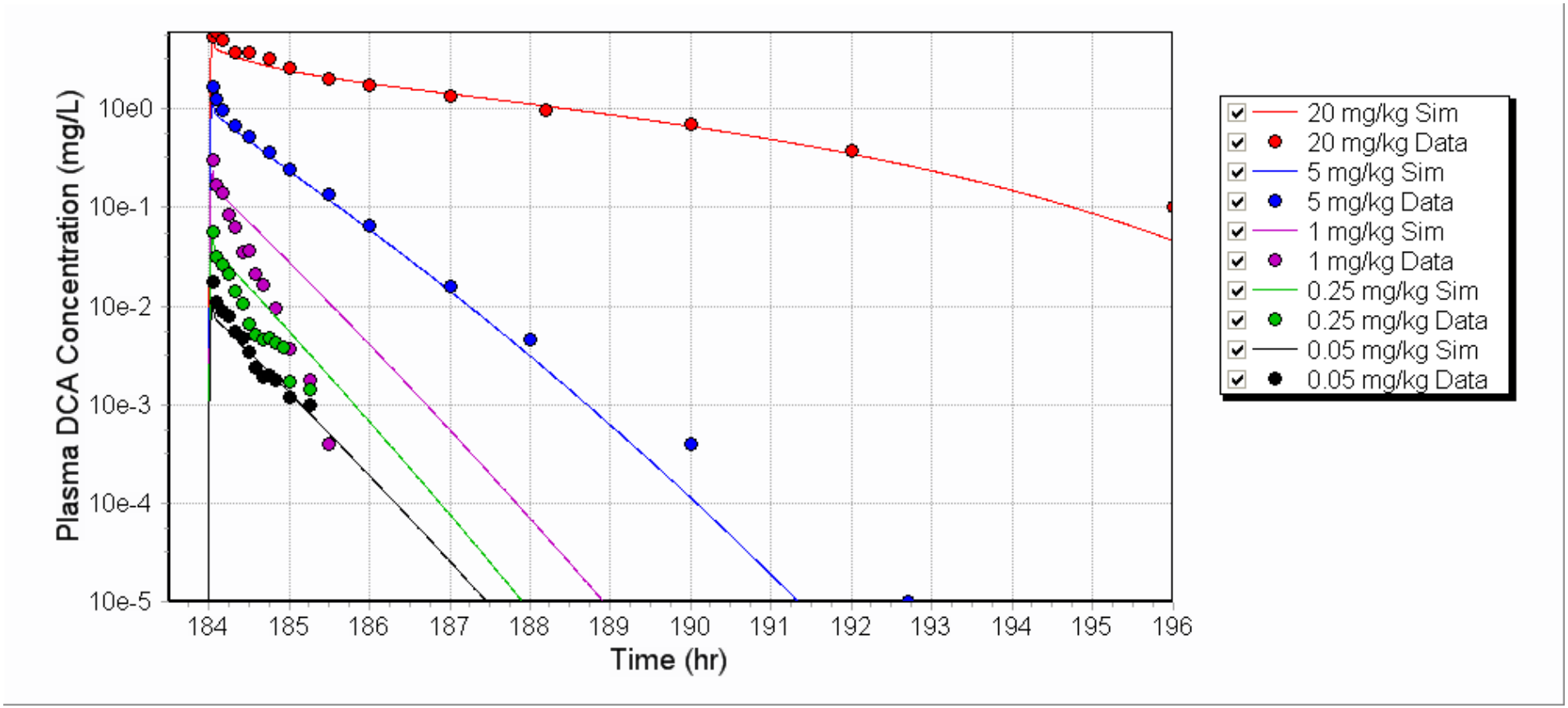


Pretreated rats received 0.2 g / L of DCA in drinking water for 7 days

Saghir, SA; Schultz, IR. (2002) Low-dose pharmacokinetics and oral bioavailability of dichloroacetate in naive and GST .-depleted rats. Environ Health Perspect 110,757-763

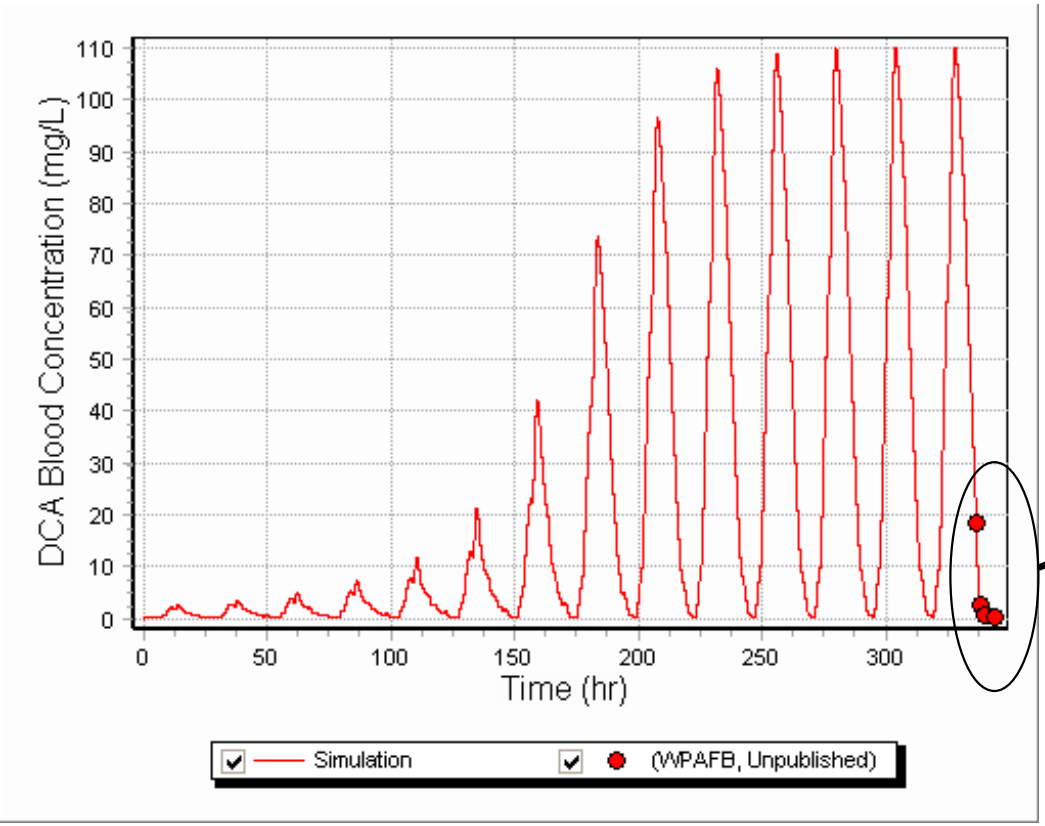
Rat DCA PBPK Model

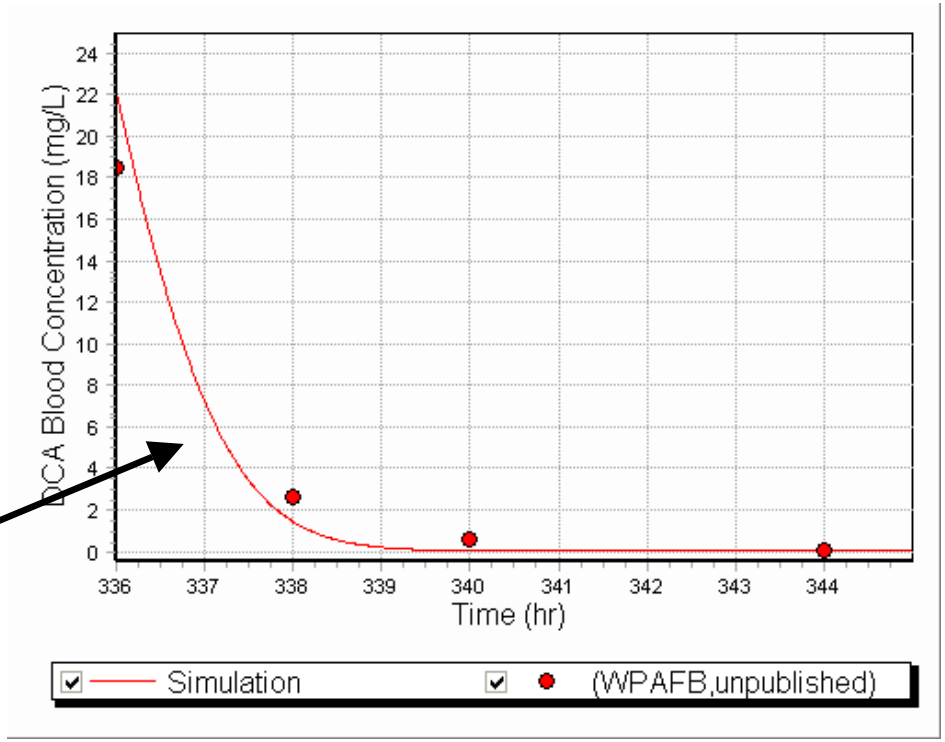
- Pre-treated rats received 0.2 g/l DCA in drinking water for 7 days (Saghir and Schultz, 2002)



Mouse DCA Drinking Water Simulations

- Pre-treated mice received 2 g/l DCA in drinking water for 14 days and then pure non-DCA water



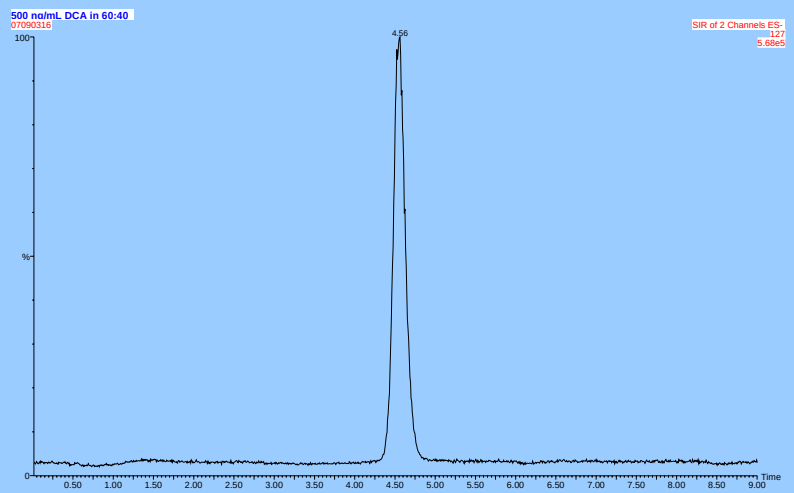


TCE→ → DCA
Metabolic pathway?
Quantitative estimates of formation?

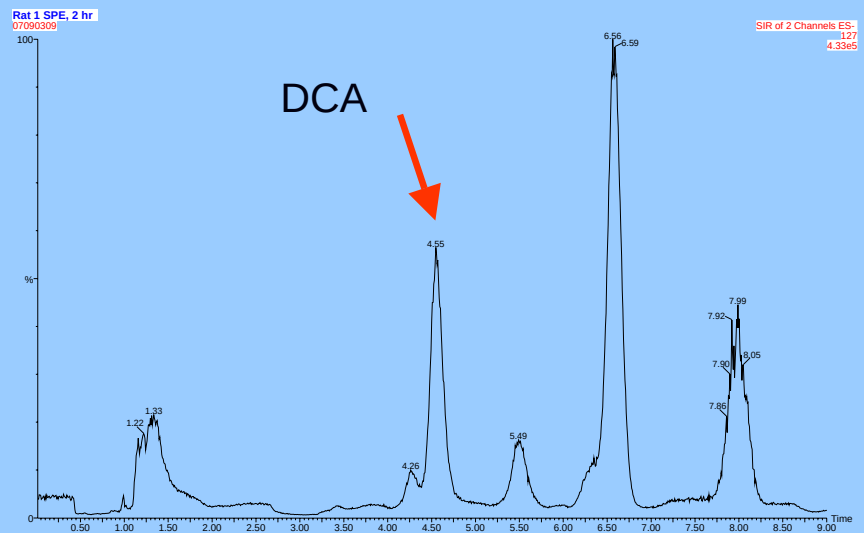
Analytical (LC/MS/MS method) Dr. Michael Bartlett and Amy Dixon, manuscript in press for analytical method in water, Animal work ongoing

Rats dose by oral bolus gavage with 2 g/kg of TCE

500 ppb DCA in water



Liver



Harmonization of Clewell et al. and Fisher et al. models from EHP 2000 Monograph on TCE

Project underway with US EPA technical involvement to create a single PBPK model for TCE and metabolites.