Science Question #3: Susceptibility of Mice to Gastrointestinal Toxicity

- ## Overview
  - *Pharmacokinetic factors that impact susceptibility*
    - Specifies differences
  - *New Data*
  - *Ongoing Studies*

SUMMIT
TOXICOLOGY

Species Differences in Pharmacokinetic Factors: Impact on Relative Susceptibility

- Stomach Lumen Transit
  - *Mouse<Rat<Human*
  - *Species differences in gastric transit would make mice more susceptible than other species*
- Number of reducing agent pools in gastric contents
  - *Mice & Rats: 2 or 3 pools, based on modeling of ex vivo data (Proctor et al., 2012)*
    - Ascorbate: mice and rats can make their own
  - *Humans: 1 pool, based on modeling of ex vivo data (Kirman et al., 2013)*
    - Available human data are limited
    - Ascorbate: humans cannot make their own
 - *Key question: Are there species differences in the number of reducing agent pools? or is this an artifact of limited human data?*

SUMMIT TOXICOLOGY

Study Design

- Fed gastric samples obtained from 7 individuals (obtained from Dr. Silvio de Flora)

- In order to provide information on multiple pools, we've modified the study protocol to include a split spike of Cr(VI)

  - *Estimate sample capacity (single spike ~3 mg/L)*

    - Measure Cr(VI) at 240 minutes

  - *Split spike run*

    - 1st Cr(VI) spike at time=0: ~0.1 mg/L to characterize rate & capacity at low concentrations; Measure Cr(VI) at 0.25, 5, 20 minutes

      2nd Cr(VI) spike at time=30min: ~3 mg/L to characterize rate & capacity at high concentrations; Measure Cr(VI) at times 90, 150 minutes

SUMMIT
TOXICOLOGY

Split-spike sample approach is yielding very useful data (data for volunteer 14 shown): Black line/Blue Diamonds = Split spike run; Red line/diamond = capacity run
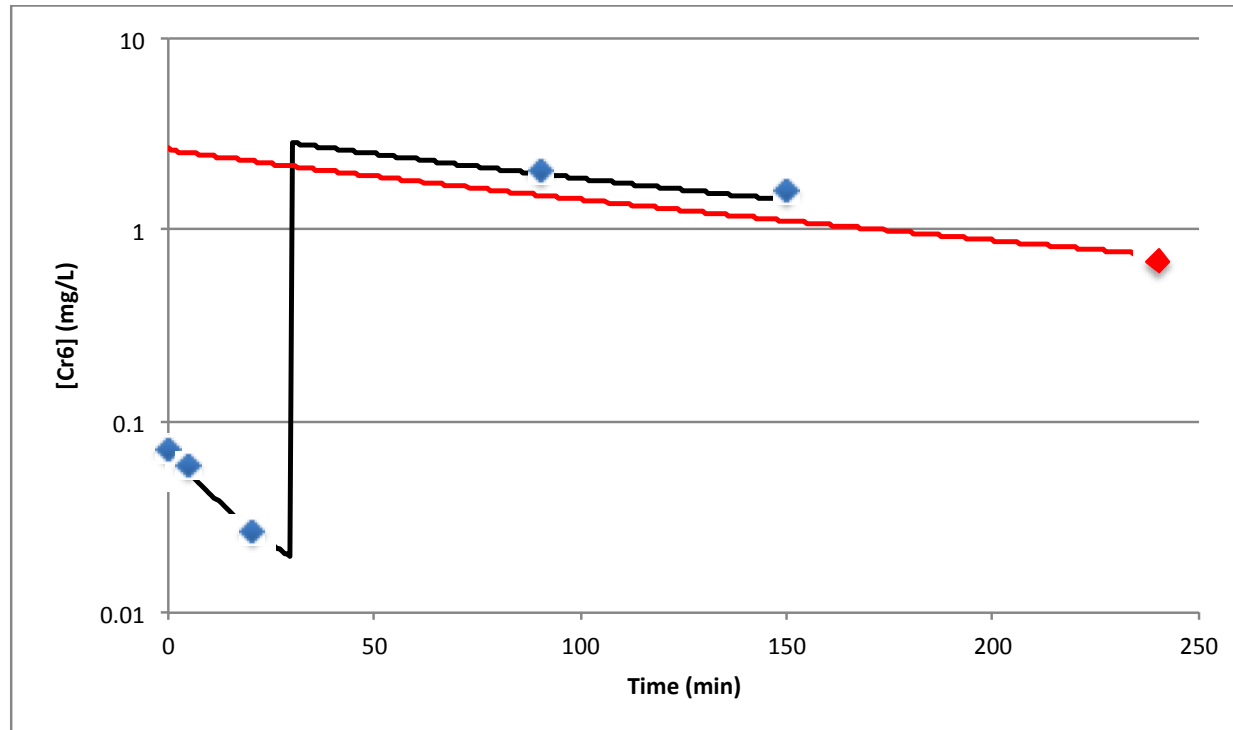

- *The slopes of the curves for time points <30 minutes are much different than for time points >30 min.*
- *Low concentrations of Cr(VI) are more rapidly detoxified than high concentrations*

Similar results obtained for all 7 samples, which are consistent with the presence of at least 2 pools: (1) fast reaction rate with small capacity (<1 mg/L); (2) slow reaction rate with large capacity (~infinite)
Without the split spike, the fast rate would not be easily detected and the slower/higher capacity reducing pool gets lost due to detection limit issues

SUMMIT
TOXICOLOGY

pH Dependence: Reducing Uncertainty at High pH

pH range important for characterizing fed state (all ages) & neonates; but only a single data point available

- k vs pH
- modeled exp(-pH)
- -- Alternative Model 1
- -- Alternative Model 2
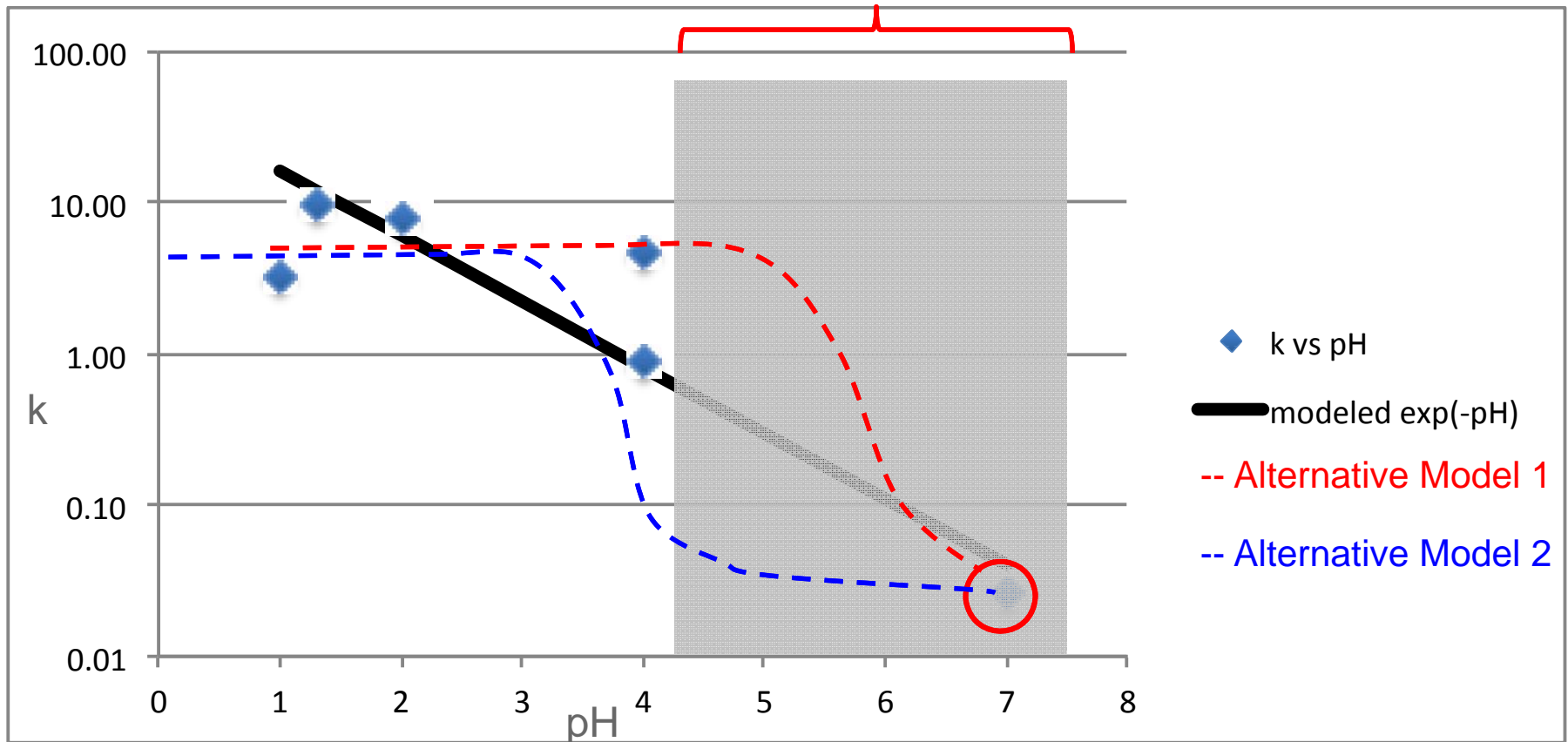
2 fed samples, adjusted to 2 pH levels (5,6)
3 PPI samples, unadjusted pH (~5,6,7)

5 additional data points for characterizing elevated pH range

SUMMIT
TOXICOLOGY