A physiologically based pharmacokinetic (PBPK) model was developed for the conazole fungicide triadimefon (TFN) and its primary metabolite, triadimenol (TNL). Rat tissue/blood partition coefficients and metabolic constants were measured in vitro for both compounds. Kinetic time course data for parent and metabolite were collected from several tissues after intravenous administration of TFN to male Sprague–Dawley rats. The model adequately simulated peak blood and tissue concentrations but failed to predict the observed slow terminal clearance of both TFN and TNL from blood and tissues. Two hypotheses were explored as possible explanations of this slow clearance: low capacity high-affinity protein binding of parent and metabolite in blood and tissues, and reverse metabolism of TNL to TFN in the liver. Model predictions were significantly improved in both hypothetic scenarios. The original model as well as both alternate models were extrapolated to humans using in vitro metabolite constants measured in human hepatic microsomes. Human equivalent doses (HEDs) were calculated for all three models for a rat NOAEL dose of 11.7 \( \mu \text{mol/kg/day} \) using area under the concentration curve (AUC) in brain and blood for TFN and TNL as dosimetrics. All dosimetric-based HEDs were above the oral reference dose of 0.11 \( \mu \text{mol/kg/day} \).

**Conclusions**

- Simulations by the original model insufficiently predicted terminal phase kinetics of TFN and TNL disposition.
  - For TFN, data indicated lingering concentrations near 1 \( \mu \text{mol/L} \) for most tissues, while model predictions were markedly lower.
  - For TNL, model predictions were marginally better, but still under-predicted observed data.
- The binding model provided marked improvements to simulations, but required many estimated parameters.
  - Heavily reliant on single pharmacokinetic data set.
  - Unique binding parameters for each compartment constitutes a biologically unlikely explanation.
- Sensitivity analyses found parameters relating to binding to be sensitive in addition to initial model sensitive parameters.

- The reversible metabolism model had improved fidelity to the observed data.
  - Required no additional estimated parameters.
  - Increased fidelity is anticipated upon experimental measurement of TNL oxidation.
- Sensitivity analyses found the oxidation kinetic parameters to be sensitive in addition to those parameters sensitive in the original model.

- Upon extrapolation of all three models to humans, predicted HEDs to the critical rat NOAEL were all above the oral AID for TFN.
  - Models not validated in humans due to lack of sufficient data.
  - Many HEDs for original and binding models were within an order of magnitude of the RID, indicating a need for further investigation.

**Future Directions**

- Test model generated hypotheses experimentally
  - Measure oxidation rates for TFN in liver and kidney microsomes
  - Investigate the capacity for macromolecular binding in rat blood and tissues
  - As data becomes available, validate the model for use in humans
- NHANES
- Occupational data

**References**


**Methods**

- **EXPERIMENTAL**
  - Microsomal metabolism studies
  - Measured Michaelis–Menten representation of concentration vs. time data on TFN depletion and TNL formation
  - Male SD rats (Crowell et al., 2010)
  - Human Male

- **In vitro partition coefficient measurement**
  - Method adapted from Jepson et al., 1994
  - Male rat tissues – blood, liver, brain, kidney, fat

- **COMPUTATIONAL**
  - Initial model development (Figure 1)
  - Model refinement
  - Blood and tissue binding (Figure 2)
  - Reversible metabolism (Figure 3)

- **APPLICATION**
  - Dose metric calculation from critical study NOAEL
  - Oral exposure to 11.7 \( \mu \text{mol/kg/day} \) SD rats
  - 12 h constant intake per day, to steady state
  - AUC and AID for TFN and TNL
  - Extrapolation to humans
  - 3 x 30 minute meals per day, to steady state
  - Human equivalent doses (HEDs) for each metric
  - Compared to oral RfD of 0.1157 \( \mu \text{mol/kg/day} \)

- **SENSITIVITY ANALYSES (Figure 7)**
  - Normalized sensitivity coefficients (NSCs) calculated:
    - NSC = (Parameter - Parameter Reference) / Parameter Reference
    - NSCs >0.15 relevant, >1.0 capable of amplifying error