CHAPTER IV
CONCLUSIONS AND RECOMMENDATIONS

This research applies chemical reaction engineering principles and mass balance equations to organ compartments to develop a predictive model for the alcohol metabolism and its major metabolites in mammals. The preliminary model predictions using literature values of the parameters are in excellent agreement with simultaneous experimental measurement of the ethanol and acetaldehyde concentrations as a function of time. This work supports the need for multicompartment models to describe the alcohol pharmacokinetics instead of the traditional one compartment model with zero-order elimination. The reverse ADH reaction is essential to keep the concentration of acetaldehyde below toxic limits and is critical in developing PBPK model for alcohol metabolism. Although the initial results are very encouraging, it is now time to critically examine all assumptions and aspects of our model to learn how it can be modified and applied to a wide range of individuals and conditions. A complete parameter sensitivity in human and small animals has to be carried out to identify the parameters that need to be known more precisely and to set experimental conditions in mice and rats to further test assumption in our PBPK model. Currently, we can predict simultaneously the blood ethanol and acetaldehyde concentrations as well as rate of formation of acetate. While acetate concentration time-trajectory data is virtually nonexistent in humans it does exist in rabbits. We will develop a PBPK model for alcohol metabolism in rabbits and then scale up to human beings. A major difference between acetate decomposition and ethanol/acetaldehyde decomposition is that ethanol and acetaldehyde are primarily metabolized in the liver while acetate is mainly metabolized in the peripheral tissues. Further it will be interesting to see the effect of alcohol in the brain compartment. Once the robustness and the best parameters are obtained, the individual variability can also be addressed by conducting Monte Carlo Simulations. Oral and intravenous administration, or fed and fasted state might require different pharmacokinetics. Appropriate statistical analysis is needed to isolate between and within subjects components of variation. Variability in ethanol pharmacokinetics originates from the non linear nature of ethanol disposition and a

combination of both genetic and environmental factors. More work is needed to document variability in ethanol pharmacokinetics in real world situation.