CHAPTER I
INTRODUCTION

Alcohol ingestion is the cause of many medical problems. Numerous attempts have been made to model alcohol metabolism using pharmacokinetic models since the inception of Widmark (1932) pseudo-zero order elimination process. Physiologically based pharmacokinetic (PBPK) modeling is a well established modeling approach in toxicology. Existing models are not self consistent for both ethanol and acetaldehyde as they violate the stoichiometry of the series reactions in ethanol metabolism. When ethanol is consumed, it passes from the stomach and intestines into the blood, a process called absorption. Ethanol cannot be excreted and must be metabolized, primarily by the enzymes in the liver. A cytosolic enzyme, alcohol dehydrogenase (ADH), mediates the conversion of ethanol to acetaldehyde. Acetaldehyde then enters the mitochondria and is rapidly converted to acetate by acetaldehyde dehydrogenase (ALDH) enzyme and eventually metabolized to carbon dioxide and water. Acetaldehyde is highly toxic and its exposure leads to fatty liver syndrome, cardiac arrhythmia (Condouris and Havelin, 1987), nausea, anxiety, and facial flushing (Sellers, *et al.,* 1981). Acetaldehyde forms adducts with proteins, nucleic acids and other compounds, the results of which are the toxic side effects (the hangover) associated with alcohol consumption. The ADH and ALDH catalyzed reactions also leads to the reduction of NAD+ to NADH (Nicotinamide Adenine Dinucleotide). The metabolic effects of ethanol intoxication stem from the actions of enzymes ADH and ALDH and the resultant cellular imbalance in the NADH/NAD+. Ethanol consumption leads to an accumulation of NADH. This high concentration of NADH inhibits gluconeogenesis by preventing the oxidation of lactate to pyruvate. In fact, the high concentrations of NADH will cause the reverse reactions to predominate, and lactate will accumulate. The consequences may be hypoglycemia and lactic acidosis. The NADH glut also inhibits fatty acid oxidation. The metabolic purpose of fatty acid oxidation is to generate NADH for ATP generation by oxidative phosphorylation, but an alcohol consumer's NADH need's are met by ethanol metabolism. In fact, the excess NADH signals that conditions are right for fatty acid synthesis. Hence, triacylglycerols accumulate in the liver, leading to a condition

known as fatty liver. Further, liver mitochondria can convert acetate into acetyl CoA in a reaction requiring ATP. However, further processing of the acetyl CoA by the citric acid cycle (TCA) is blocked, because NADH inhibits two important regulatory enzymes- isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. The accumulation of acetyl CoA has several consequences. First, ketone bodies will form and be released into the blood, excerbating the acidic condition already resulting from the high lactate concentration. The processing of the acetate in the liver becomes inefficient, leading to the buildup of acetaldehyde. This very reactive compound form covalent bonds with many important functional group in proteins, impairing protein function. If ethanol is consistently consumed at high levels, the acetaldehyde can significantly damage the liver, eventually leading to cell death. The NADH produced in the cytosol by ADH must be reduced back to NAD+ via either the lactate-pyruvate interconversion via lactic dehydrogenase, the malate-aspartate shuttle or the glycerol-phosphate shuttle. Thus, the ability of an individual to metabolize ethanol is dependent upon the capacity of hepatocytes to carry out either of these two shuttles, which in turn is affected by the rate of the tricarboxylic acid (TCA) cycle in the mitochondria whose rate of function is being impacted by the NADH produced by the ALDH reaction.

Liver damage from excessive ethanol consumption occurs in three stages. The first stage is the development of fatty liver. In the second stage- alcoholic hepatitis-groups of cell die and inflammation results. This stage can itself be fatal. In stage three-cirrhosis-fibrous structure and scar tissue are produced around the dead cells. Cirrhosis impairs many of the liver's biochemical functions. The cirrhotic liver is unable to convert ammonia into urea, and blood levels of ammonia rise. Ammonia is toxic to the nervous system and can cause coma and death.

1.1 Significance of Research

Understanding alcohol metabolism to help prevent or decrease incidents of acute toxicity is the main focus of this research. The development of a predictive model that could be used for quantitative analysis of alcohol metabolism in normal and alcoholic subjects is an important problem. Of particular significance is the

combination of biochemical reaction kinetics and physiologically based pharmacokinetic modeling approaches. A predictive model for alcohol metabolism in normal and ALDH2 deficient individuals and mammals is important because it allows for 1) an analysis to be carried out to better understand the effects of gender, age, body temperature, 2) the prediction of the direction and the rate of the concentration-time trajectories of ethanol, acetaldehyde and acetate in a subject from two blood alcohol samples, 3) the application of the model to mammals for quantifying studies that can predict and correlate with such things as the time after administration at which mice lose their righting reflex or become anesthetized, 4) the PBPK model could be extended to develop a model for emergency room guidelines for methanol poisoning by ethanol injection. If these aims are achieved, then the model can provide a quantitative basis of evaluating deleterious effects of alcohol metabolism. Also, the use of mathematical modeling in metabolism for clinical evaluation will be advanced. Which could predict or guide measurements in practical setting (e.g., Emergency Rules) to advance biological simulation theory or practice.

1.2 Research Objectives

To develop a physiologically based pharmacokinetic model for ethanol and acetaldehyde metabolism in human being