A Preliminary Physiologically Based Pharmacokinetic Model for Naphthalene and Naphthalene Oxide in Mice and Rats

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Abstract—Naphthalene is a toxicant with unusual species and tissue specificity that has been the subject of in vitro studies. We describe a preliminary physiologically based pharmacokinetic (PBPK) model for naphthalene constructed solely from in vitro data for comparison to animal data without the use of adjustable parameters. The prototypical PBPK model containing five lumped tissue compartments was developed to describe the uptake and metabolism of naphthalene by mice and rats dosed intraperitoneally (ip) and orally (po). The model incorporates circulation and biotransformation of the semistable reactive intermediate, naphthalene oxide, as well as the parent compound naphthalene. Circulation is included because the toxic action of naphthalene has been proposed to be caused by the formation of a reactive metabolite in one organ (liver) and its circulation to another organ (lung) being adversely affected by the metabolite. The model allows conversion of naphthalene oxide into dihydriodiol, glutathione (GSH) conjugates, 1-naphthol (non-enzymatically) and covalently bound adducts with proteins. Model simulations are compared with previously reported in vivo measurements of glutathione depletion, mercapturic acid formation, and covalently bound protein formation. The mouse model predicts accurately the amount of mercapturates excreted, the effect of various pretreatments, and the extent of covalent binding in the lung and liver resulting from ip administration, including the sharp increase in binding between 200 and 400 mg/kg.

Keywords—PBPK, Circulating metabolites, Glutathione, Mathematical modeling.

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) models are useful tools to study the toxicology of chemicals, particularly those with species and tissue specificity (for general information, see 6 and 29). Although PBPK models have been applied to a wide variety of compounds, they have not been used with naphthalene, a common environmental pollutant. To simulate naphthalene toxicology, the activation of naphthalene to the reactive intermediate, naphthalene oxide, in the liver and its subsequent circulation to the lung and further biotransformation must be considered. Although other PBPK models include the production and metabolism of intermediate compounds, none describe the generation of reactive products in one tissue, depletion of cofactors involved in detoxification, circulation of the metabolite, and reaction of the metabolite in a second tissue. A PBPK model that is a multicompartmenal, physiological model with these characteristics is needed for naphthalene.

Several existing models have many of these characteristics. In a PBPK model for carbon tetrachloride toxicokinetics (45), the metabolites are included, but the model structure is not physiological. A benzene model (41) includes the assumption that the benzene oxide produced in the liver is metabolized rapidly, but no benzene oxide is removed in the effluent blood. In an inhalation model (2) for carbon monoxide (CO), CO is produced endogenously and by biotransformation of dichloromethane in the liver. The CO then complexes with hemoproteins thus producing carboxyhemoglobin. However, in this model, CO is restricted to the blood compartment.

A few models describe the distribution of parent and daughter compounds throughout the body. The fate of methyl mercury and its demethylation product, inorganic mercury, has been described (23). Dermal penetration by hexachlorobiphenyl and the distribution of the parent compound and its metabolites also have been discussed (25). Two butadiene (BD) models (35,40) incorporate the oxidation of BD to butadiene monoepoxide (BMO) in the lung and liver and BMO oxidation, hydrolysis, and GSH conjugation in the liver. A PBPK model for styrene (17) is modeled after one of the butadiene models (35), therefore, it includes oxidation in the lung and liver, further metabolism of the oxide in the liver, and circulation of the oxides.

A thorough review of naphthalene toxicology, espe-
cially of tissue and species specificity in rodents, has been presented (8). Some of the reactions involved in naphthalene biotransformation (the reactions included in this model) are shown in Fig. 1. The GSH status of the tissues is important in naphthalene toxicology, and a modified version of a model for GSH depletion and resynthesis developed previously (22) has been incorporated as a sub-component of the overall PBPK model.

Sufficient in vitro data for mouse and rat tissues exist to construct a preliminary PBPK model for naphthalene and the naphthalene oxides. In this study, we describe a PBPK model constructed from the literature without adjustable parameters.

DEVELOPMENT OF MODEL

Model Structure

The model structure is depicted in Fig. 2. The reactive metabolites, that is, the two naphthalene oxide enantiomers, circulate throughout the body. The model essentially is a system of parallel PBPK models that are bridged by the biotransformation of naphthalene to naphthalene oxide in the lung and liver. All five tissue compartments (lung, liver, kidney, fat, and other tissues) are assumed to be well mixed and equilibrated with the exiting blood. For compounds of sufficient lipophilicity, the assumption that there is no substantial barrier to diffusion into the organ generally is valid (19) and commonly is employed (23,35,40). It is further assumed that the transit time through the tissue (on the order of seconds or minutes) is insignificant compared with the time scale of the experiments to be modeled (hours). The mass balance equations, which describe tissue concentrations of naphthalene, the naphthalene oxides, and GSH, are the core of the model. As better experimental data accumulate, the model parameters may need revision, but the general structure incorporating circulating naphthalene oxide should still apply. The rates of naphthalene oxide conversion to dihydrodiol, NO-GSH conjugates, naphthol, and covalently bound naphthalene metabolites are included to provide additional information from the simulation. Equations describing the whole animal system appear in Appendix A. The differential equations are integrated numerically using LSODA (Livermore Solver for Ordinary Differential Equations, with Automatic Switching Method for Stiff and Non-stiff Problems).

Determination of Parameters

Physiological. The physiological parameters calculated for a 22-g mouse and a 220-g rat are summarized in Table 1.

Partition Coefficients

With the use of partitioning characteristics of naphthalene in air-water (54) and octanol-water (31) systems, it is possible to predict tissue: blood partition coefficients (PCs) (1,24,26). With the use of regression equations derived from measured PCs (1), tissue: blood PCs were estimated for lung (0.627), liver (5.41), kidney (3.87), fat (796), and muscle (4.13). The PC for muscle was used for the other tissues compartment of this model. The regression equation for the lung was developed by using only non-hydrophobic solutes, and therefore, the calculated value probably is not the best estimate for naphthalene partitioning. Because other models usually use the same PC for all well-perfused tissues (21,55), a value of 4.0 (average of the PC calculated for muscle and kidney) was used in the base model instead of the calculated 0.627. Simulations