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Preliminary physiologically based pharmacokinetic models for benzo[a]pyrene and dibenzo[def,p]chrysene in rodents

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants generated as byproducts of natural and anthropogenic combustion processes. Despite significant public health concern, physiologically based pharmacokinetic (PBPK) modeling efforts for PAHs have so far been limited to naphthalene, plus simpler PK models for pyrene, nitropyrene, and benzo[a]pyrene (B[a]P). The dearth of published models is due in part to the high lipophilicity, low volatility, and myriad metabolic pathways for PAHs, all of which present analytical and experimental challenges. Our research efforts have focused upon experimental approaches and initial development of PBPK models for the prototypic PAH, B[a]P, and the more potent, albeit less studied transplacental carcinogen, dibenzo[def,p]chrysene (DBC). For both compounds, model compartments included arterial and venous blood, flow limited lung, liver, richly perfused and poorly perfused tissues, diffusion limited fat, and a two compartment theoretical gut (for oral exposures). Hepatic and pulmonary metabolism was described for both compounds, as were fractional binding in blood and fecal clearance. Partition coefficients for parent PAH along with their diol and tetraol metabolites were estimated using published algorithms and verified experimentally for the hydroxylated metabolites. The preliminary PBPK models were able to describe many, but not all, of the available data sets, comprising multiple routes of exposure (oral, intravenous) and nominal doses spanning several orders of magnitude. Supported by Award Number P42 ES016465 from the National Institute of Environmental Health Sciences.

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Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants with natural and anthropogenic sources. PAHs are generated as by-products of incomplete combustion, and are also present in many fossil fuels (e.g. crude oil, coal) (U.S.EPA, 1991b). PAHs are lipophilic and non-volatile, and are therefore found primarily in soils, sediments, and adsorbed to particulate matter in the air (Baan et al., 2009). Many PAHs are thought to be carcinogenic to animals and humans, including the prototypic PAH, benzo[a]pyrene (B[a]P), and the less well-studied, more potent dibenzo[def,p]chrysene (DBC; formerly referred to as dibenzo[a,l]pyrene).

DBC has been observed to be a highly potent carcinogen in studies in laboratory animals (Cavalieri et al., 1989, 1991; Higginbotham et al., 1993; Lavoie et al., 1993; Prahalad et al., 1997). DBC exposure has been shown to cause skin tumors in SENCAR mice exposed dermally (Cavalieri et al., 1989, 1991; Higginbotham et al., 1993; Lavoie et al., 1993), mammary tumors in Sprague Dawley rats exposed intramammarily (Cavalieri et al., 1991), and lung and liver cancers in CD-1 and A/J mice exposed intrapertioneally (Platt et al., 2004; Prahalad et al., 1997). DBC has been found to be approximately 100-fold more potent in producing lung adenomas than B[a]P (Prahalad et al., 1997). Recently, DBC has been shown to cross the placenta in B6129SF1/J mice, causing T-cell lymphoma, lung adenoma, and liver lesions in offspring of mothers exposed to single doses of 15 mg/kg DBC (Castro et al., 2008; Yu et al., 2006). The International Agency for Research on Cancer (IARC) currently classifies DBC as a 2B, or possibly carcinogenic to humans (IARC, 2010).

Isolated from coal tar and identified in 1933, B[a]P is one of the earliest recognized and best studied chemical carcinogens (reviewed in (Phillips, 1983)). B[a]P is classified as a 2A or probable human carcinogen by the International Agency for Research on Cancer (IARC), based on the strong weight of evidence of animal carcinogenicity and mechanistic data rather than human epidemiological studies (Baan et al., 2009; IARC, 2010). While lung cancer is induced in humans by mixtures of PAHs, there is inadequate human data on exposure to B[a]P alone. Exposures to B[a]P via oral, inhalational, and dermal routes have been demonstrated to be carcinogenic in a

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variety of laboratory animals, including rodents and primates (IARC, 1973; U.S.EPA, 1991a, 1991b).

DBC and B[a]P share many similarities in their physical chemical properties, as well as their presumed mechanisms of toxicity. Both are very lipophilic, non-volatile, high molecular weight PAHs, with six and five aromatic rings, respectively. DBC and B[a]P, like most PAHs, are thought to induce carcinogenesis through the interaction of electrophilic metabolites with cellular macromolecules (e.g., DNA and proteins). Both compounds have complex metabolic pathways centering upon reactive bay and fjord regions of their structures, with diol epoxide and o-quinone metabolites as the primary carcinogenic metabolites (Fig. 1) (Xue and Warshawsky, 2005). While cytochrome P450 (CYP) enzymes play an important role in each of their metabolic pathways, the responsible isoforms appear to vary for each chemical: CYP1A1 and CYP1B1 isoforms both contribute significantly to the oxidation of B[a]P, while CYP1B1 appears to be more relevant in the oxidation of DBC (Conney, 1982; Gelboin, 1980; Shimada et al., 1999). CYP1A1 has little constitutive expression, but is highly inducible in many tissues, including lung and liver (Dey et al., 1999). CYP1B1 is constitutively expressed in lung and a variety of hormonal tissues (e.g., adrenal, thymus, ovary, testes, and mammary glands), and is also inducible in liver tissue (Buesen et al., 2002; Walker et al., 1995; Zhang et al., 2003).

Physiologically based pharmacokinetic (PBPK) models are mathematical descriptions of physiology and biochemistry that facilitate extrapolations between different organisms and exposure scenarios. In recent years, PBPK models have been used increasingly in the risk assessment process to provide a link between laboratory studies and human toxicity, as well as a quantitative basis for developing human exposure limits. Despite the ubiquity and toxicity of many PAHs, PBPK models for the vast majority of these compounds, particularly those of higher molecular weight, have not been developed. Indeed, with the exception of models for lower molecular weight PAHs, such as pyrene (Haddad et al., 1998) and naphthalene (Willems et al., 2001), there are no well explicated PBPK models for any member of this family of compounds, perhaps because of the experimental challenges associated with their high lipophilicity and low volatility, or their complex and extensive metabolism that presents both analytical and model development challenges. No PBPK models exist in the literature for DBC, despite its potency and potential transplacental carcinogenicity. The only published PBPK model for B[a]P in rodents is rudimentary (Roth and Vinegar, 1990), while those described for humans have not been evaluated against any pharmacokinetic data (Chiang and Liao, 2006; Ciffroy et al., 2011).

In this paper, we present pharmacokinetic data for DBC administered orally in female B6129SF1/J mice, the same strain of mice used in transplacental carcinogenicity studies, as well as preliminary PBPK models for DBC and B[a]P in rodents. While development of the preliminary DBC model is the primary goal of this work, because of the insufficient data available in the literature, as well as the

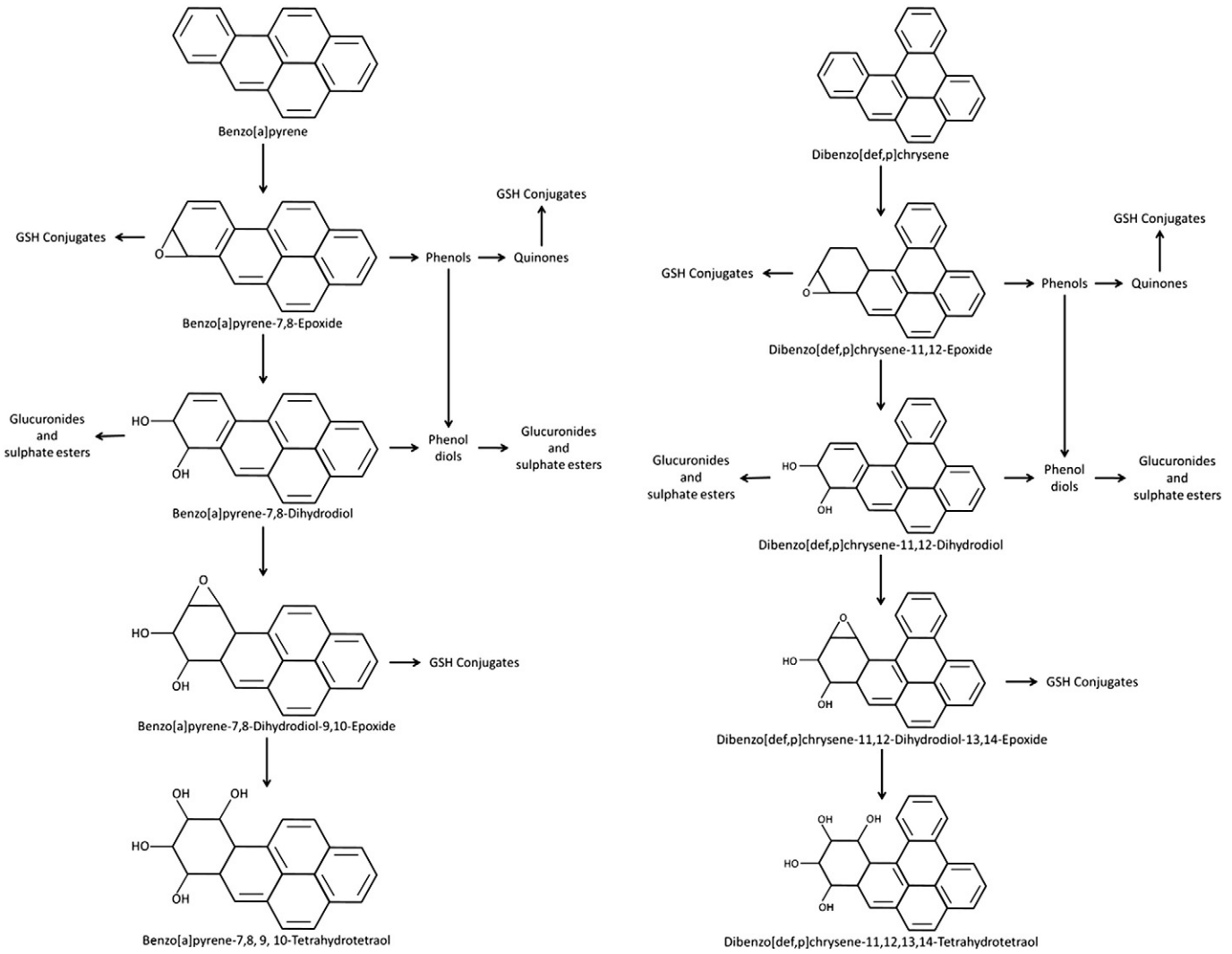

Fig. 1. Major metabolic pathways for benzo[a]pyrene and dibenzo[def,p]chrysene.