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Development of an integrated multi-species and multi-dose route PBPK model for volatile methyl siloxanes – D4 and D5

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ABSTRACT

There are currently seven published physiologically based pharmacokinetic (PBPK) models describing aspects of the pharmacokinetics of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) for various exposure routes in rat and human. Each model addressed the biological and physicochemical properties of D4 and D5 (highly lipophilic coupled with low blood: air partition coefficient and high liver clearance) that result in unique kinetic behaviors as well differences between D4 and D5. However, the proliferation of these models resulted in challenges for various risk assessment applications when needing to determine the optimum model for estimating dose metrics. To enhance the utility of these PBPK models for risk assessment, we integrated the suite of structures into one coherent model capable of simulating the entire set of existing data equally well as older more limited scope models. In this paper, we describe the steps required to develop this integrated model, the choice of physiological, partitioning and biochemical parameters for the model, and the concordance of the model behavior across key data sets. This integrated model is sufficiently robust to derive relevant dose metrics following individual or combined dermal and inhalation exposures of workers, consumer or the general population to D4 and D5 for route-to-route, interspecies and high to low dose extrapolations for risk assessment.

1. Introduction

Cyclic volatile methyl siloxanes (cVMSs), such as octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5), are low molecular weight silicones used in the manufacture of high molecular weight silicone polymers and in cosmetics and personal care products, leading primarily to low level inhalation and dermal exposures to both workers and consumers. The hazard profile of these cVMSs have been extensively evaluated (Dekant and Klaunig, 2015; in this issue; REACH, 2011a, b). To understand the influence of kinetic factors on delivered dose of these cVMSs, our teams have conducted a comprehensive set of kinetic studies over the last several years (Tables S–1). In association with these time course data sets, we also developed several PBPK models describing the biological and physical–chemical processes regulating the kinetic disposition of either D4 or D5 in various species after different routes of exposure (Andersen et al., 2001; Reddy et al., 2003; Sarangapani et al., 2003; Reddy et al., 2007, 2008) (Tables S–2). Kinetic data and associated models were also derived to evaluate the disposition of D4 following implantation (Thrall et al., 2008) but were not used for our model development. The individual models focused on specific data sets in order to describe the kinetic behavior of either D4 or D5 in rats or humans following various routes of administration.

The first modeling work for cVMSs with D4 (Andersen et al., 2001) utilized data from a series of inhalation kinetic studies in the rat (Plotzke et al., 2000). This initial PBPK analysis uncovered a suite of processes that regulate siloxane kinetics in the rodent that

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differ from those at work with inhalation of most other volatile organic compounds. Among those characteristics were low blood: air partitioning, high fat: blood partitioning, high metabolic clearance by the liver, and slower loss of D4 from tissues than expected for simple well-mixed, flow-limited uptake compartments. In addition, a discrepancy between the rate of D4 elimination via exhalation and the associated blood levels following inhalation exposure indicated the presence of a pool of D4 in the plasma that was not available for exhalation. These observations led to inclusion of several 'deep-tissue compartments' to account for slow, multiphasic loss after cessation of exposure, a pool (compartment) in blood assumed to represent lipoproteins, called a mobile lipid pool (MLP), and multiple fat compartments to describe the longer-time exhalation curves indicative of slower release of D4 from fat compartments. Sarangapani et al. (2003) expanded the Andersen et al. (2001) model to include a kinetic description of D4 following oral and dermal exposure.

D5 has even greater lipophilicity and lower blood: air partitioning than D4. Successful curve fitting with D5 time course data (Tobin et al., 2008) required addition of other deep tissue compartments, including a deep tissue store within the blood itself (Reddy et al., 2008). Thus, the rat D5 inhalation description had the largest number of tissue compartments of all the cVMSs PBPK models. The *in vitro* dermal absorption and *in vivo* dermal exposure studies in rats (Jovanovic et al., 2008) and the human volunteer inhalation studies (Utell et al., 1998) lacked the detailed tissue time courses required for establishing the presence and characteristics of deep tissue compartments. However, the dermal studies did provide information to characterize the dynamics of uptake at the skin surface while the human inhalation studies provided time-course information for metabolites to determine the pathways and time course of elimination of various low molecular weight metabolites (Utell et al., 1998). Overall the human modeling efforts for D4 and D5 adequately simulated the time-course biomarker data of D4 and D5 collected during inhalation or dermal exposure (Reddy et al., 2007).

Although each of the contributions on PBPK modeling with D4 and D5 produced good correspondence between model predictions and available data sets, the compartmental structures of these models varied according to specific data sets and the goals of model development. Unquestionably, the existence of multiple models enhances the ability to capture behaviors in the individual studies. Conversely, their proliferation presents some challenges for various risk assessment applications where it becomes difficult to determine the optimum model for estimating specific dose metrics. To improve the use of these PBPK models for risk assessment, we built a single integrated multi-compound, and multi-dose (MC-MD) route PBPK model for cVMSs that preserved the key chemical-specific biological and kinetic features determined in previous PBPK models. This contribution describes the steps required to develop this unified model, the choice of physiological, partitioning and biochemical parameters for the model, and the concordance of the model behavior across key data sets.

2. Methods

We used a three step process to construct a multi-compound, multi-dose route model for cVMSs that included 1) combining inhalation rodent model structures across compounds 2) coordinating model across species 3) combining routes of exposure. Table 1 shows the key model features incorporated into the current model compared to those used previously. The current computer code uses a nested algorithm to toggle specific tissues on or off depending on the chemical, the animal species and exposure route. The mass balance equations that describe the rate of change of D4 and D5 and their metabolites in various tissues are in the supplemental material (S-4). Computer code, specific scripts that reproduce all figures in this manuscript and associated documentation can be obtained from the corresponding author (TSM). The series of differential equations were solved by numerical integration using the Gear Algorithm for stiff systems in acslX version 11.8.4 (AEgis, Technologies Group, Inc, Huntsville, Alabama, USA).

2.1. Step 1: Combining the inhalation rodent model structures across compounds (D4 and D5)

As a first step, we developed a single compartmental suite for D4 and D5 based on inhalation exposures (Fig. 1a–d) using the structure from the rat D5 inhalation model (Reddy et al., 2008) and modified parameters and compartments for D4 based on earlier work. With D5, we retained all model features from Reddy et al. (2008) with the exception of metabolism. D4 exhibited saturable hepatic metabolism around the highest concentration (700 ppm) (Sarangapani et al., 2003). At the highest exposure concentration (160 ppm) of D5, blood concentrations were approximately 10-fold lower than D4 concentrations (Reddy et al., 2008), indicative of first-order metabolism. For the purposes of developing a common model structure across compounds, we included saturable metabolism into the D5 structure. This integrated PBPK model has six tissue compartments including blood, fat, lung, liver, slowly perfused tissues, and rapidly perfused tissues.

Physiological parameters (Table 2) such as ventilation rate [L/hr] and tissue blood flow rates (as percentage of cardiac output, L/hr) were from Brown et al. (1997). The scaling function used for the metabolism parameters and the ventilation rate was changed from $BW^{0.7}$ to $BW^{0.75}$ to provide consistent scaling throughout the model. Starting values for the chemical specific model parameters were adopted from the previous published models and re-parameterized, if necessary, by comparing the model simulations with experimental data. All model parameters were separately estimated for male and female with the exception of the partition coefficients. The data sets and decisions made in developing the integrated model are outlined below.

2.1.1. Datasets

For both D4 and D5 kinetic studies (Plotzke et al., 2000a; Tobin et al., 2008), parent test material was synthesized with a theoretical maximum of one ^{14}C radio-labeled carbon attached to each silicon atom. After exposure and tissue collection, concentrations of parent test material were measured in blood and select tissues and total radioactivity was determined in blood and the same tissues. In addition, radioactivity was measured in urine, feces, expired air and "remaining carcass." The concentration of total metabolites was the difference between total radioactivity and the parent material concentrations.

D4: The tissue time-course data for total radioactivity and parent chemical from ^{14}C-D4 inhalation studies in male and female rats were collected following a single 6-h exposure 7, 70, or 700 ppm or multiple exposures for 6 h/day for 15 days to 7 or 700 ppm of D4 (Plotzke et al., 2000a). Exhaled breath, blood, liver, fat, lung, urine, and feces were used to construct the model. The PBPK model structure had two different fat compartments. In our current model structure, simulations for the concentration in the "distributed" fat were compared to the fat tissue data rather than the "diffuse fat" as was done previously.

D5: The tissue time-course data for total radioactivity and parent chemical from ^{14}C-D5 inhalation studies in male and female rats were collected following a single 6-h exposure to 7 or 160 ppm or following multiple exposures (160 ppm) for 6 h/day for 15 days. The data used for determining model parameters included exhaled