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Are highly lipophilic volatile compounds expected to bioaccumulate with repeated exposures?

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ABSTRACT

With non-volatile compounds, high lipophilicity (i.e., fat:blood partition coefficients, Pf, in the range of several hundred to a thousand or higher) typically leads to concerns for bioaccumulation. To evaluate the extent to which highly cleared, lipophilic vapors are expected to accumulate in blood and tissues, we conducted pharmacokinetic (PK) analysis, using both a generic physiologically based (PBPK) model for inhalation of volatile compounds (VCs) and a more detailed PBPK model specifically developed for a highly lipophilic volatile (decamethylcyclopentasiloxane, D_5). The generic PBPK model for inhalation of VCs in humans showed that highly metabolized, lipophilic compounds, with a low blood:air partition coefficient (Pb), do not accumulate in blood or systemic tissues with repeat exposures although a period of days to weeks may be required for fat to reach periodic steady state. VCs with higher Pb (in the hundreds) and lower hepatic extraction accumulate in blood on repeat exposures. The more detailed PBPK model for D_5 also showed that this lipophilc VC does not accumulate in blood and predictions of the increases in D_5 in fat with repeat exposures in rats agreed with experiments. In general, the major characteristic favoring accumulation of VCs in blood and systemic tissues is poor whole-body clearance, not lipophilicty. The term bioaccumulation should be used to refer to cases where repeat exposures lead to increases in VC blood (or central compartment) concentration. Based on this definition, highly cleared VCs, such as D_5, would not be considered to bioaccumulate on repeat exposures.

1. Introduction

Octamethylcyclotetrasiloxane (D_4) and decamethylcyclopentasiloxane (D_5), two volatile methyl siloxanes (VMS), are highly lipophilic, cyclic silicone fluids (Fig. 1; Table 1). Often, a high order of lipophilicity is considered to be a key property in deciding if a compound has the potential to bioaccumulate upon repeated exposures. However, the broader question of bioaccumulation of volatile compounds (VCs) with large octanol:water partition coefficients (usually referred to as $\log K_{o/w}$) has not been systematically examined. In this work, we first use a generic human PBPK model to examine factors such as blood:air partition coefficient (Pb) and hepatic extraction (HE) that influence the pharmacokinetic (PK) behavior of VCs upon repeat inhalation exposures. This generic PBPK model analysis specifically permitted the evaluation of the role of these factors in accounting for differential accumulation in blood, body tissues, and fat on repeat exposures for various VCs. After application of the generic VC model to assess factors affecting blood and tissue accumulation, the predicted behavior from the generic modeling effort was evaluated by examining fat tissue time course behavior in rats exposed daily for 6-h/day to D_5 for periods up to 6 months.

In contrast to simpler model structures for compounds such as styrene (Ramsey and Andersen, 1984), pharmacokinetic models with D_5 (Reddy et al., 2007) required deep tissue compartments filled by diffusion of D_5 from the tissue themselves and another pool of bound D_5 in blood. The need for these additional compartments presumably arises because of increasing storage of D_5 in lipid depots within the body. Fat concentrations of D_4 and D_5 have been reported in rats exposed for 6 months, 5 days/week, 6-h/day (Tobin et al., 2008). The PK results from these longer duration studies allow direct examination of accumulation potential of VMS. Comparisons of time course tissue data from rats exposed to D_4 or D_5 daily by inhalation over a period of 6 months with PBPK model simulations were used to assess the validity of conclusions from the generic model regarding accumulation in blood for

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Nomenclature

BW	body weight
C_a	concentration of free D_5 in arterial blood exiting lungs
C_{blood}	concentration in venous blood
C_{ex}	concentration of D_5 or VC in exhaled air
C_{fat}	concentration in fat
C_{in}	inhaled concentration of D_5 or VC
D_4	octamethylcyclotetrasiloxane
D_5	decamethylcyclopentasiloxane
$K_{o/w}$	octanol:water PC
Pb	blood:air PC
PC	partition coefficient
Pf	fat:blood partition coefficient
QC	cardiac output
QL	fraction of cardiac output to liver
S.D.	standard deviation
t	time
VMS	volatile methyl siloxanes
VC	volatile compounds

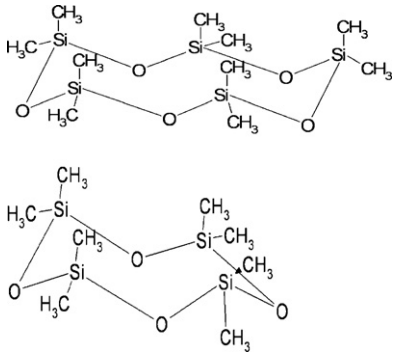

Fig. 1. The chemical structures of decamethylcyclopentasiloxane (D5) and octamethylcyclotetrasiloxane (D4).

highly lipophilic, well-cleared VCs. Our studies provide the basis for several recommendations for improving the definitions of 'bioaccumulation' in reference to VCs.

2. Materials and methods

2.1. A Generic PBPK model for volatile compounds

A generic model based on the styrene PBPK model structure (Ramsey and Andersen, 1984) was used to examine repeat inhalation exposures (Fig. 2). This model simulated inhalation exposures to a concentration of a VC in the ambient air, C_{in}. Elimination of the VC was by hepatic metabolism and by exhalation. The physiological parameters were set to appropriate values for a reference human (Table 2). The method of Poulin and Krishnan (1995) was used to calculate liver:blood, muscle:blood, and fat:blood partition coefficients (PCs) based on a given value of $K_{o/w}$. Although this method for estimating PCs was developed for rat tissue PCs, the PCs for rat tissue and human tissue are expected to be similar (Gargas et al., 1989). The slowly perfused compartment:blood PC was set to the muscle:blood PC. The richly perfused tissue:blood PC was set to the liver:blood PC.

The effect of metabolic clearance was examined by running the model with various values of hepatic extraction (HE), which is defined as the intrinsic hepatic clearance (V_{max}/K_m) divided by the sum of the intrinsic hepatic clearance and the blood flow to the liver. This generic model was also used to examine the relationship between PK behavior and Pb. The exhalation clearance, CL_{ex}, is a function of Pb (Reddy et al., 2003):

$$CL_{ex} = \frac{QP}{Pb + QP/QC} \quad (1)$$

where QC is cardiac output and QP is alveolar ventilation.

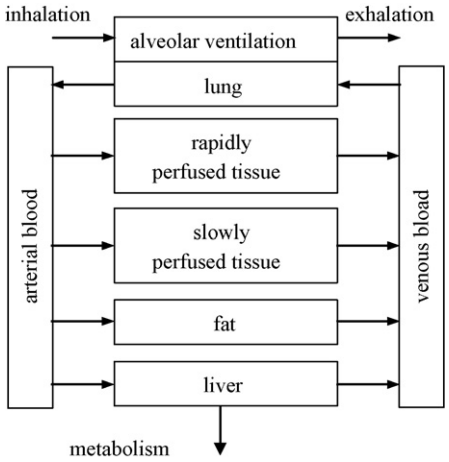

Fig. 2. Schematic diagram of the generic PBPK model for inhalation of volatile compounds in humans. The fat tissues were treated in one of two ways as: (a) one compartment with flow-limited uptake, or (b) one compartment with diffusion-limited uptake.

Table 1
Chemical and pharmacokinetic properties of D_4 and D_5

	D_4	D_5
CAS number	556-67-2	541-02-6
Molecular formula	$C_8H_{24}O_4Si_4$	$C_{10}H_{30}O_5Si_5$
Molecular weight (Da)	296.6	370.8
Vapor pressure at 25 °C (mmHg)	1.05[a]	0.2[a]
In vivo plasma:air PC for rats	0.85[b]	0.26[c]
In vitro whole blood:air PC for rats	4.31[b]	0.72 ± 0.20[c]
In vitro perirenal fat:air PC for rats	2089[b]	1436 ± 325[c]
In vitro fat:blood PC for rats	485[d]	1990[d]

[a] Provided by the Dow Corning Corporation.
[b] From Andersen et al. (2001).
[c] From Reddy et al. (2007).
[d] Estimated by dividing the perirenal fat:air PC by the whole blood:air PC.

Table 2
Physiological parameters used in the human PBPK model

Parameter	Value
Physiological properties	
Body weight (kg)	70
Cardiac output, QC (liters/hr)	372[a]
Alveolar ventilation, QP (liters/hr)	300[a]
Fraction of blood flow to tissues	
Liver	0.227
Fat	0.052
Rapidly perfused tissue	0.472
Slowly perfused tissue	0.249
Fraction of body weight in compartments	
Liver	0.0314[b]
Fat	0.23[b]
Rapidly perfused tissue	0.05[b]
Slowly perfused tissue	0.5396[b]
Blood	0.059[b,c]

[a] From Arms and Travis (1988).
[b] From (Brown et al., 1997). The sum of the fraction of body weight in each compartment is 0.91 because 9% of the body was assumed to receive minimal blood flow. The specific gravity of all tissues was estimated to be 1.
[c] The arterial and venous blood compartments were estimated to contain 35% and 65% of the blood volume, respectively.