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Development of a human physiologically based pharmacokinetic (PBPK) model for dermal permeability for lindane

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HIGHLIGHTS

- Two estimation methods are compared for dermal skin patch data parameters.
- Incorporating molecular weight improves dermal permeability fits.
- Protein binding is essential for prediction of steady-state permeability.

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ABSTRACT

Lindane is a neurotoxicant used for the treatment of lice and scabies present on human skin. Due to its pharmaceutical application, an extensive pharmacokinetic database exists in humans. Mathematical diffusion models allow for calculation of lindane skin permeability coefficients using human kinetic data obtained from *in vitro* and *in vivo* experimentation as well as a default compound-specific calculation based on physicochemical characteristics used in the absence of kinetic data. A dermal model was developed to describe lindane diffusion into the skin, where the skin compartment consisted of homogeneous dermal tissue. This study utilized Fick's law of diffusion along with chemical binding to protein and lipids to determine appropriate dermal absorption parameters which were then incorporated into a physiologically based pharmacokinetic (PBPK) model to describe *in vivo* kinetics. The estimation of permeability coefficients using chemical binding in combination with *in vivo* data demonstrates the advantages of combining physiochemical properties with a PBPK model to predict dermal absorption.

1. Introduction

The US Environmental Protection Agency (US EPA) has the responsibility to determine human health risk from exposure to chemical compounds that may be environmental contaminants. However, limited financial resources are available to perform traditional toxicological screens on all potentially toxic chemicals. With the development of efficient high-throughput (HT) *in vitro* techniques, a strategy has been created to correlate toxicity with HT measurements. This has become the US EPA's ToxCast research program, motivated by a chemical prioritization framework flexible enough to incorporate new data as they become available (Wambaugh et al., 2013). Since it is not feasible to obtain experimental data for all chemicals, this program also relies on predictive toxicology methodology, where chemicals are prioritized for further testing based on physicochemical characteristics and their potential for biological disruption of key pathways. The US EPA National Center for Computational Toxicology (NCCT) has already conducted essential research needed to correlate chemical characteristics and biological activity as listed in the ToxCast database, developed in phases and currently containing over 2000 chemicals. An integrative modeling framework will become essential in this predictive toxicology paradigm – one that integrates exposure, dose, and toxicity for many chemicals. Up to this point, physiologically based pharmacokinetic (PBPK) models have been used to convert environmental exposure to an internal (target) dose for a single chemical at a time. As the application of PBPK modeling has

Abbreviations: PBPK, physiologically based pharmacokinetic modeling; HT, high-throughput; SC, stratum corneum.

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become more accepted, a trend has emerged to include PBPK modeling as part of an overall computational strategy. Current efforts to merge PBPK modeling with exposure modeling describing populations use different routes of exposure (Isaacs et al., 2014). Dermal exposure is one of the most common types of exposure, particularly for pesticides, water-borne chemicals, and consumer products.

Lindane was used as an agricultural insecticide until December 2006, when the US Environmental Protection Agency canceled registration of agricultural products containing this chemical (U.S. EPA, 2006). This decision was due in part to the negative effect on the central nervous system: lindane binds to GABA receptors, leading to increased excitability of these neurons (Suñol et al., 1989; Tusell et al., 1987). This binding causes both acute and chronic effects such as convulsions and seizures even at low doses (Gilbert, 1995). Recently, lindane has been upgraded to a human carcinogen by IARC (Loomis et al., 2015). Prior to this, the US Food and Drug Administration approved the use of a 1% lindane solution for the treatment of head lice and scabies (US Food and Drug Administration, 2009), albeit with a warning about potential toxicity and a recommendation for use only as a second tier treatment. Due to its use in humans as a therapeutic agent, particularly children, extensive studies have been conducted to determine the time course of lindane disposition. To produce data relevant to pharmaceutical skin applications, human kinetic studies have used dermal exposure as the entry route for lindane (Dick et al., 1997). Availability of a human dermal database and its potential toxicological effect on different life stages and populations make lindane an excellent choice for a modeling study.

The skin is a complex organ consisting of stacked layers composed of a combination of lipophilic and protein-rich tissues. Compartmental models simulating different layers have been used to describe a chemical's penetration (Bookout et al., 1996; Stahl et al., 2012). Dermal penetration is a function of both the chemical's properties such as lipophilicity, and the composition of the application vehicle. Despite the biological complexity, penetration can be modeled using the fundamental diffusion process (Fick's law). This physical law indicates that movement of the chemical across the skin is proportional to the gradient in chemical concentration, where the proportionality constant is the diffusion constant. The goals of the present work were: (1) to obtain estimates for the dermal diffusion constant based on physicochemical and biochemical properties, (2) to use a PBPK model for lindane in combination with an *in vivo* dataset to optimize for the dermal diffusion constant in humans, and (3) to find a method to calculate dermal absorption which could be generalized to other ToxCast compounds.

2. Methods

2.1. Experimental human data

In vivo time-course data were obtained from published literature (Dick et al., 1997). Dermal absorption of lindane in a white spirit vehicle (indicated as Formulation A) was measured in blood plasma at fixed time points after exposure on the forearms of several volunteers. Six hours post-exposure, the skin was wiped of all remaining lindane. Venous blood samples were taken from the unexposed arm until 80 h post-exposure and plasma samples were analyzed for lindane concentrations. The experiment utilized a finite dosing scheme; no additional chemical was applied to the surface of the skin as absorption occurred.

2.2. Dermal constants

This study utilized a homogenous compartmental model assuming both a well-mixed vehicle compartment and a well-mixed skin compartment. Diffusion is the main mechanism governing penetration of the chemical into the skin through the stratum corneum (SC) into the main dermal compartment. This can be mathematically described using Fick's one-dimensional diffusion equation:

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial l^2}\right). \tag{2.1}$$

Here, C is the chemical concentration, D is the diffusion constant, and l represents the diffusional distance of the chemical (here, assumed to be skin depth). In addition, the solubility between the vehicle and the SC is assumed to be constant, and is given as the dermal partition coefficient P_{der}. This constant is different for each chemical and is calculated as described below.

The default method used by the US EPA for calculating the permeability coefficient K_p is given by the Potts-Guy Potts and Guy (1992) equation:

$$\log K_p = -2.8 - 6.0 \cdot 10^{-3} \cdot (MW) + 0.74 \cdot \log P_{ow}. \tag{2.2}$$

This permeability equation can also be modified to predict the dermal partition coefficient P_{der} by separating Eq. (2.2) as described by Cleek and Bunge (1993):

$$\log P_{der} = 0.74 \cdot \log P_{ow}, \tag{2.3}$$

and

$$\log\ \mathrm{Dl} = -2.8 - 6.0 \cdot 10^{-3} \cdot (MW). \tag{2.4}$$

However, binding to plasma proteins, particularly albumin, is not incorporated into Eq. (2.2). As an adaptation, this study utilized equations in Chen et al. (2015) to calculate the following: the vehicle:water ($P_{v:w}$), SC:water ($P_{sc:w}$), and dermis:water ($P_{der:w}$) partition coefficients; the vehicle:dermal partition coefficient P_{der}; the diffusion constant D; and the permeability coefficient K_p. The following equations (Eqs. (2.5)–(2.7)) are used to calculate the partition coefficient between the vehicle and the dermis, P_{der} (Eq. (2.8)):

$$P_{v:w} = 4.62 \cdot P_{o:w}^{0.55}, \tag{2.5}$$

$$P_{sc:w} = \frac{\rho_{lipid}}{\rho_{water}} \cdot P_{ow}^{0.69}, \tag{2.6}$$

$$P_{der:w} = 0.7\left(0.68 + \frac{0.32}{f_u} + 0.025 \cdot P_{sc:w}\right), \tag{2.7}$$

$$P_{der} = P_{der:w}/P_{v:w}. \tag{2.8}$$

Here, P_{ow} is the chemical octanol:water partition coefficient, ρ_{lipid} is lipid density, ρ_{water} is water density, and f_u represents the fraction of lindane not bound to albumin (Chen et al., 2015). Taking into consideration binding to albumin, the generalized diffusion constant is as follows:

$$D\ \ (\mathrm{cm}^2/\mathrm{h}) = \left[\frac{10^{(-8.15-0.655\cdot\log(MW))}}{0.68 + \frac{0.32}{f_u} + 0.025 \cdot P_{sc:w}}\right] \cdot 3.6{\times}107. \tag{2.9}$$

During the steady-state portion of dermal exposure, the relationship between different constants becomes linear with respect to each other. This in turn, makes calculation of these constants from experimental data easier. These relationships among constants have been summarized by Lehman (2014):

$$K_p\ \ (\mathrm{cm/hr}) = \frac{P_{der}D}{l}, \tag{2.10}$$

where K_p is the permeability coefficient and l is the diffusional path length.