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Evaluation of deltamethrin kinetics and dosimetry in the maturing rat using a PBPK model

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ABSTRACT

Immature rats are more susceptible than adults to the acute neurotoxicity of pyrethroid insecticides like deltamethrin (DLM). A companion kinetics study (Kim et al., in press) revealed that blood and brain levels of the neuroactive parent compound were inversely related to age in rats 10, 21, 40 and 90 days old. The objective of the current study was to modify a physiologically based pharmacokinetic (PBPK) model of DLM disposition in the adult male Sprague–Dawley rat (Mirfazaelian et al., 2006), so blood and target organ dosimetry could be accurately predicted during maturation. Age-specific organ weights and age-dependent changes in the oxidative and hydrolytic clearance of DLM were modeled with a generalized Michaelis–Menten model for growth and the summary equations incorporated into the PBPK model. The model's simulations compared favorably with empirical DLM time-courses in plasma, blood, brain and fat for the four age-groups evaluated (10, 21, 40 and 90 days old). PND 10 pups' area under the 24-h brain concentration time curve (AUC_{0-24h}) was 3.8-fold higher than that of the PND 90 adults. Our maturing rat PBPK model allows for updating with age- and chemical-dependent parameters, so pyrethroid dosimetry can be forecast in young and aged individuals. Hence, this model provides a methodology for risk assessors to consider age-specific adjustments to oral Reference Doses on the basis of PK differences.

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Introduction

Pyrethroid insecticides represent an increasing proportion of pesticide sales in the United States and other nations in recent years (Bekarian et al., 2006). Pyrethroids' popularity stems from their insecticidal potency, slow development of pest resistance, and relatively low acute toxicity of most compounds in mammals (Soderlund et al., 2002). Agricultural and household use of pyrethroids has increased substantially with the tightening of restrictions on sales of organophosphates. Heudorf et al. (2004) found pyrethroid metabolites in 75% of an urban German population without occupational contact. Pyrethroid exposure has been widely documented in pregnant women, infants and children by several groups of investigators (Berkowitz et al., 2003; Lu et al., 2006; Morgan et al., 2007; Tulve et al., 2006, 2008; Yáñez et al., 2002). To better understand the pharmacokinetics (PK) of these compounds, we have investigated the metabolism (Anand et al., 2006a, 2006b) and *in vivo* PK (Kim et al., 2008, in press) of the pyrethroid deltamethrin (DLM) in the rat. PK data for the adult rat were used to develop a physiologically based PK (PBPK) model of DLM disposition (Mirfazaelian et al., 2006).

PK is a complex phenomenon with concurrent absorption, tissue distribution, metabolism, and elimination processes determining the target organ dose of toxic moiety over time, and in turn the magnitude and duration of toxicity (Caldwell et al., 1995). Anatomical, physiological and metabolic changes that occur as a child grows alter these processes and thus target organ dosimetry and adverse effects of chemicals (Bruckner, 2000; Clewell et al., 2004; Ginsberg et al., 2002). Sheets et al. (1994) observed that preweanling and weanling rats were much more sensitive to DLM acute neurotoxicity than adults. Some 15 years later Anand et al. (2006a) and Kim et al. (in press) provided *in vitro* and *in vivo* evidence that inefficient metabolic inactivation of DLM by the pups was a major contributor to relatively

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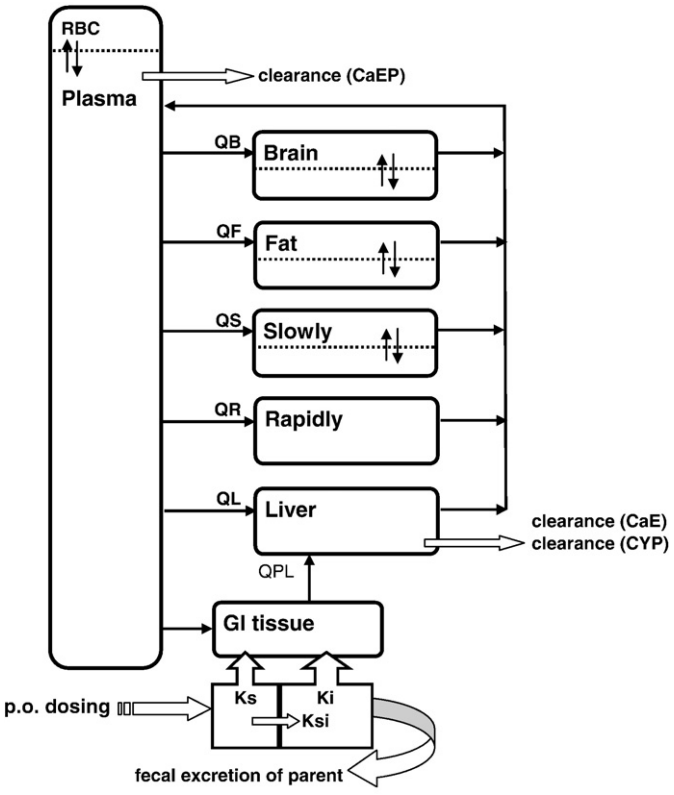

Fig. 1. Schematic of the 7-compartment PBPK model of DLM for immature rats. Delivery of DLM to the liver, GI tract and rapidly perfused tissues is flow-limited, while delivery to the remaining tissues (brain, erythrocytes, fat and slowly perfused tissues) is diffusion-limited.

Table 1
Chemical-specific parameters for PBPK models of DLM in rats.

	Value
Partition coefficients[a]	
Liver/plasma	0.44
Fat/plasma	48.7
GI/plasma	0.44
Brain/plasma	0.22
Slowly perfused/plasma	5.59
Rapidly perfused/plasma	0.44
Erythrocyte/plasma	0.17
Tissue permeability area-cross product (fraction of tissue flow (Qt, l/h))	
Fat(PA_F)[a]	0.02
Brain(PA_{BRN})[b]	0.008
Slowly(PA_S)[a]	0.7
Metabolic rate constants[c]	
Liver cytochrome P450 (CYP)	
V_{max1} (mg/h/kg$^{0.75}$)	See Appendix A
K_{m1} (mg/l)	See Appendix A
Liver carboxylesterase (CaE)	
V_{max2} (mg/h/kg$^{0.75}$)	See Appendix A
K_{m2} (mg/l)	See Appendix A
Plasma carboxylesterase (CaEP)	
V_{max3} (mg/h/kg$^{0.75}$)	See Appendix A
K_{m3} (mg/l)	See Appendix A
Fecal excretion (h^{-1})[b]	
K_{FE}	0.1
Uptake rate constants (h^{-1})[a]	
Gastric absorption (Ks)	0.01
Intestinal absorption (Ki)	0.90
Gastrointestinal transfer rate (Ksi)	0.70

[a] Mirfazaelian et al. (2006).
[b] Fitted.
[c] Anand et al. (2006a, 2006b).

Table 2
Physiological parameters for PBPK models for DLM in rats.

	Value
Parameter	
Cardiac output (l/h/kg$^{0.75}$)	14.1[a]
Body weight	experimental
Tissue plasma flows (% plasma cardiac output)[b]	
Fat	7
GI	13.6
Brain	2
Liver (arterial)	2
Liver (portal)	15
Slowly perfused	15
Rapidly perfused	59
Plasma volume fractions (% tissue)[c]	
Brain	1.51
Fat	2.49
Slowly perfused	2.00
Blood	0.51
Tissue volumes (% body weight)	
Blood	7.4[b]
Liver, GI, fat, brain, richly and slowly perfused	See Table 1, Appendix A

[a] Delp et al. (1991).
[b] Mirfazaelian et al. (2006).
[c] Brown et al. (1997) (blood volume fractions) and see Appendix A Equation for plasma volume fraction (PVj).

high brain and blood DLM concentrations and toxicity. Additional age-dependent PK processes may also be involved in the susceptibility of the immature animals.

A number of risk assessment authorities have advocated the development of PBPK models to account for the unique, changing characteristics of infants and children (Daston et al., 2004; Landrigan et al., 2004; Ginsberg et al., 2004a). PBPK modeling allows incorporation of age-specific information on multiple factors that can influence PK. PBPK models have been developed for a limited number of pharmaceuticals in children (Bjorkman et al., 1998; Ginsberg et al., 2004b). Empirical drug data may be available in such instances for model calibration and validation, but age-specific physiological and biochemical input values for healthy children are often lacking. Fat volumes and tissue blood flow rates, metabolic rate constants and alveolar volumes, for example, had to be estimated by Price et al. (2003) to model inhaled furan. In other efforts, Rodriguez et al. (2007) developed what they termed a life-stage model to simulate blood levels of six environmental contaminants in children and adults. Age-dependent metabolism of the environmental agents was inputted according to age-specific liver cytochrome P450 (CYP2E1) content. While this approach is expedient, it assumes that metabolic clearance of the substrate is exclusively due to CYP2E1. Nong et al. (2006) made the same assumption in modeling inter-child

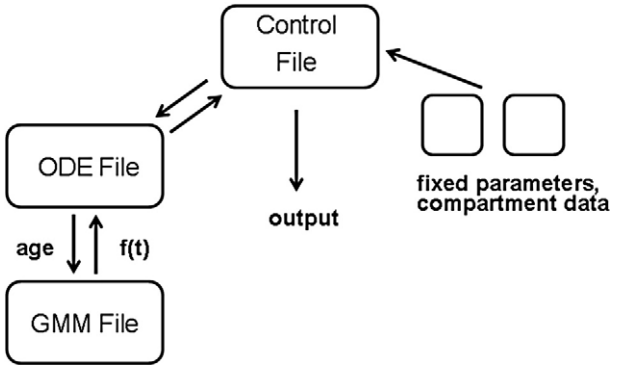

Fig. 2. The coupling of the PBPK model and GMM equations. The PBPK simulation starts with a set of simulation conditions and a fixed set of parameters passed to the ODE file. Age-dependent parameters ($f(t)$) are updated by the GMM file during the course of the simulation.