Modeling Dermal Diffusion and Metabolism for Consumer Products

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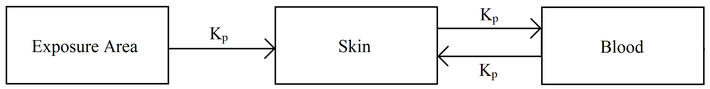
1. Background

- Dermal absorption is a route of exposure for consumer products and is investigated by the EPA
- Metabolism contributes to clearing chemicals from the skin
- Mathematical modeling is an efficient method for estimating toxicity for thousands of chemicals
- Modeling has been used to determine absorption, but not metabolism parameters
- A model incorporating diffusion and metabolism could yield more accurate toxicity predictions

2. Methods

2.1 Multi-Compartment Model

- Models the movement of concentration of chemical among Exposure Area, Skin, and Blood
- Chemicals transition among compartments at rate $K_p\ (cm\ h^{-1})$



2.2 Michaelis-Menten Metabolism Equation

- Describes the rate of conversion of a chemical to its metabolite
- V_{max}: maximum reaction rate of the system; K_m: substrate concentration at half of V_{max}

$$\nu = \frac{V_{max}C}{K_m + C}$$

2.3 Linear Regression

- Obtained regression line for cumulative amount versus hours post dose data
  - Estimate K_p using slope and t_{lag} as x-intercept

$$K_p = \frac{\beta_1}{C_v} \qquad D = \frac{L^2}{6t_{lag}} \qquad P_{cv} = \frac{LK_p}{D}$$

K_p: Permeability Coefficient, D: Diffusivity Coefficient, P_{cv}: Partition Coefficient

2.4 Fick's 2nd Law of Diffusion

- Describes diffusion of chemical concentration with respect to time and position in skin
- Numerical methods were used to solve model for concentration profiles

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

2.5 Model

- Solves for concentration of chemical at depths of the skin over time
- Model for diffusion and metabolism of the applied chemical:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \frac{V_{max}C}{K_m + C}$$

- Model for diffusion and metabolism of produced metabolite:

$$\frac{\partial M}{\partial t} = D\frac{\partial^2 M}{\partial x^2} + \frac{V_{max}C}{K_m + C}$$

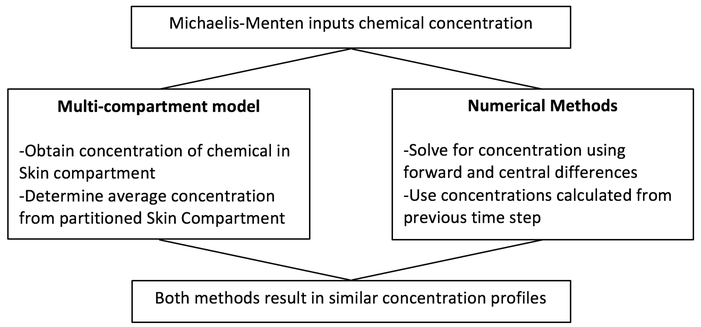
3. Results

3.1 Obtaining Parameters for Carboxyl-vanillylnonanamide (C-VN)

- Linear portion of amount penetrated versus time data indicates system reached steady state
- Calculating regression line from data points in steady state reduced error

	$K_p\ (cm\ h^{-1})$	$t_{lag}\ (h)$	$D\ (cm^2 h^{-1})$	P_{cv}	Error
Complete Time Course	3.78E-4	7.50	1.39E-5	6.80E-1	296.45
Linear Time Course	4.18E-4	12.26	8.50E-6	1.23	3.74

3.2 Determining Chemical Concentration



3.3 Sensitivity of Metabolism Parameters

- Increasing K_m by 4 orders of magnitude caused less than 1 order of magnitude change in model
- Increasing V_{max} by 4 orders of magnitude resulted in a 2 order of magnitude change in model

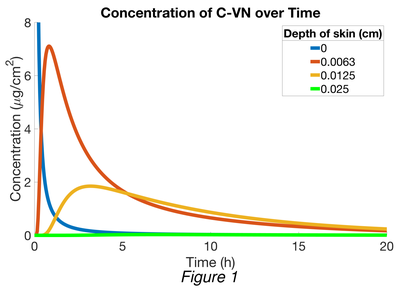


Figure 1

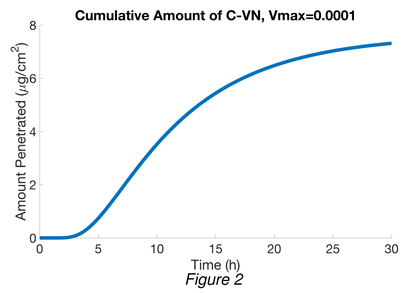


Figure 2

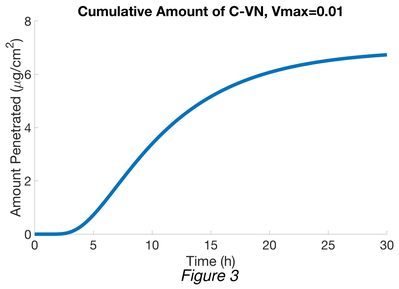


Figure 3

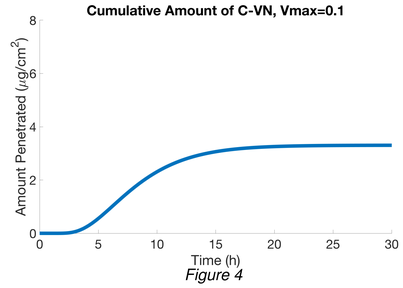


Figure 4

Figure 1: Concentration profiles for C-VN at different depths in the skin
Figure 2-4: Cumulative amount of C-VN over time for three values of V_{max}

3.4 Application of Model

- Use numerical methods to solve for Mono(2-ethylhexyl)phthalate (MEHP) concentration
- Calculate D values for MEHP and its metabolite (5-OH-MEHP) to use in model
- Optimize value of V_{max} to fit model to data of metabolite

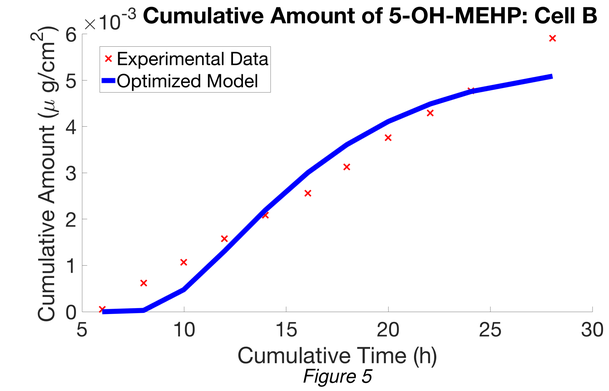


Figure 5

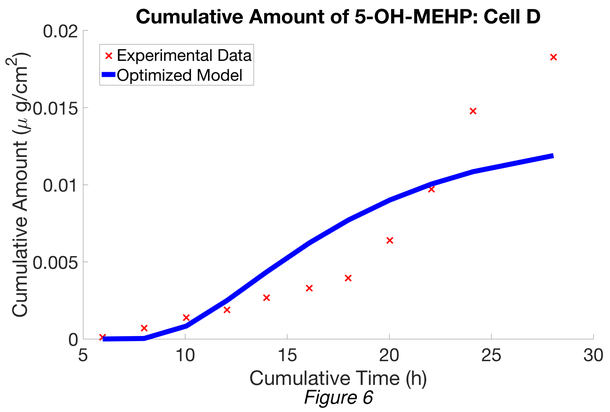


Figure 6

Figure 5 and 6: Cumulative amount of MEHP at final skin depth for two individuals

4. Conclusion

- Metabolism impacts amount of chemical diffusing to final depth of skin
- V_{max} shows high sensitivity while K_m does not
- Presence of metabolite indicates metabolism should be incorporated in model
- Expanding model to include other factors such as individual variance in metabolic enzymes could decrease error
- Obtaining experimental values for V_{max} will increase accuracy of toxicity predictions

5. Acknowledgments

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