PROPOSED SUITE OF MODELS FOR ESTIMATING DOSE RESULTING FROM EXPOSURES BY THE DERMAL ROUTE

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Abstract

Dermal absorption is an important pathway for exposure to chemicals in the residential environment that may lead to toxic effects at the portal of entry or systemically. To predict dose and potential risk associated with dermal exposures, understanding of contaminant fate and transport in skin is required. Drivers for absorption and transport in skin are a function of exposure duration, chemical properties, and metabolism.
A suite of models is presented for use in characterizing and quantifying dosimetry of toxic agents absorbed by the dermal route in order to incorporate mechanistic information into risk characterization. These range from a distributed parameter model that only considers resistance in the stratum corneum to a model that treats the entire skin system as one well-stirred compartment. The model suite provides the flexibility required to evaluate dosimetry on a variety of compounds by including the required level of resolution to incorporate rate-limiting components. The suite is demonstrated through a case study involving three phthalates: Diethylhexyl phthalate (DEHP), Diethyl phthalate (DEP), and Benzyl butyl phthalate (BBzP).

Model Overview

- Each model estimates dermal exposure by evaluating chemical concentration as a function of time in the following two compartments of the skin:
  - stratum corneum
  - viable epidermis
- For each compartment, one of 2 sets of governing equations is used. These are:
  - Diffusion based model
  - Well-mixed model
- These options create 4 possible compartment/equation combinations, which make up the first 4 models of the suite
- The final 2 models look only at the stratum corneum. These are useful when:
  - concentration in the stratum corneum is the main interest
  - the chemical is known to pass through the epidermis significantly faster
  - a single compartment model is desired
- Required inputs are molecular weight and octanol to water partition coefficient (K_{ow}).These are used to:
  - estimate remaining chemical related constants, such as the diffusion constant in each compartment
  - determine which model is best suited for the chemical

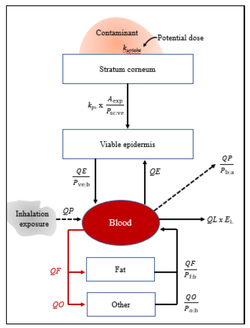

Figure 1: Example of a physiologically based toxicokinetic (PBTK) model that accounts for a potential dose of a contaminant from the dermal and inhalation routes, e.g. naphthalene. In this example (Kim et al., 2007; Kim, Andersen, & Nylander-French, 2006), k_{uptake} = input rate constant for dermal exposure; k_{pv} = permeability coefficient for the viable epidermis; A_{exp} = exposed surface area; $P_{sc:ve}$ = stratum corneum:viable epidermis partition coefficient; QE = blood flow rate to skin; $P_{ve:b}$ = viable epidermis:blood partition coefficient; QP = pulmonary ventilation rate; $P_{b:a}$ = blood:air partition coefficient; QF = blood flow rate to fat; $P_{f:b}$ = fat:blood partition coefficient; QO = blood flow rate to other tissue; $P_{o:b}$ = other tissue:blood partition coefficient; QL = blood flow rate to the liver; E_L = extraction ratio.

Diffusion Model

- The diffusion-based models treat a given compartment as a medium through which the chemical diffuses. These models
  - provide depth dependent information within the compartment
  - account for time required to diffuse through each layer
  - are computationally more demanding
- Perform better than well-mixed models for chemicals that diffuse slowly relative to the time scale of the simulation
- Molecular weight strongly influences diffusion rate
  - Large molecular weight leads to slower diffusion
- K_{ow} determines the equilibrium state across boundaries
  - Large K_{ow} leads to larger concentrations in the stratum corneum at the boundary with a hydrophilic vehicle and at the boundary with the viable epidermis

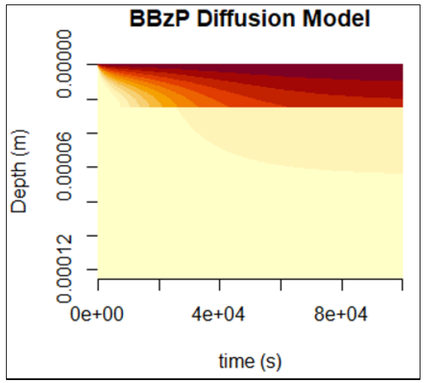

Figure 2: The stratum corneum is assumed to be 25 µm. The concentration in the viable epidermis at the boundary with the stratum corneum is much smaller than in the stratum corneum. This is caused by a large SC:VE partition coefficient, a parameter that is dependent on K_{ow}.

Well-Mixed Model

- The well-mixed models look only at the average concentration in the compartment. These models
  - are computationally less demanding
  - do not provide depth dependent information
- Perform best when the concentration is constant across the compartment or its variation with position is unimportant
- For long exposure times, the assumption that the concentration in the compartment is uniform becomes more reasonable

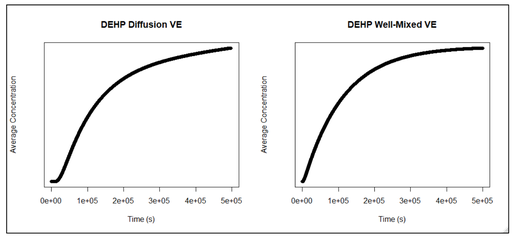

Figure 3: A qualitative comparison of the average concentration in the viable epidermis (as a fraction of the vehicle concentration) as predicted by each model.
While both curves approach an asymptote after enough time, the diffusion model shows a lag time, which corresponds to the time it takes for the chemical to diffuse through the stratum corneum. This effect is most pronounced for large chemicals, such as DEHP.

Example Governing Equations

Diffusion-Dominated Stratum Corneum (SC)

$$\frac{\partial C_{SC}}{\partial t} = D_{SC}\frac{\partial^2 C_{SC}}{\partial x^2}$$

Well-Mixed Viable Epidermis (VE)

$$A_{exp}h_{VE}\frac{d\langle C_{VE}\rangle}{dt} = -A_{exp}D_{SC}\frac{\partial C_{SC}}{\partial x}\bigg|_{x=h_{sc}} + QE\,P_{VE:b}C_{Vb} - \frac{QE}{P_{VE:b}}\langle C_{VE}\rangle$$

Definitions

h_{SC} and h_{VE} = thickness of SC and VE, respectively
D_{SC} = diffusion coefficient in SC
C_{SC} = concentration in SC
$\langle C_{VE}\rangle$ = average concentration in VE
C_{Vb} = venous blood concentration
t = time
x = position in SC

Phthalate Case Study

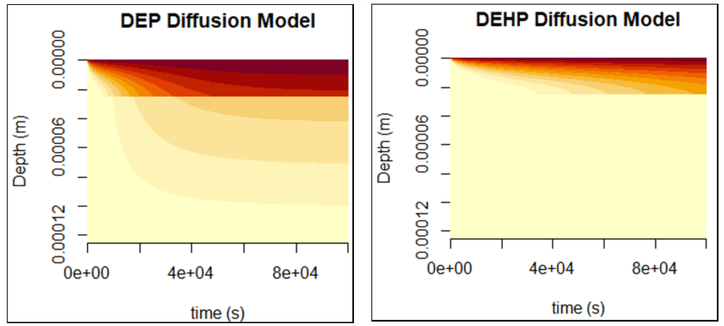

Figure 4: The diffusion model plots for the three phthalates (two above, one in Figure 2) show concentration as a function of time and depth. The dark red represents a concentration at or near that of the vehicle, whereas white represents a concentration near 0. DEP, which is the smallest of the three (see Table 3), diffuses through the stratum corneum the fastest, which is especially noticeable when comparing it to DEHP.

Phthalate	Molecular Weight (g/mol)	Log(K_{ow})
DEP	222.24	2.45
BBzP	312.37	4.82
DEHP	390.56	7.53

Table 1: Chemical parameters for the three phthalates. DEP has the lowest molecular weight and K_{ow}, DEHP has the highest of each, and BBzP has values between the other two. Being the smallest, DEP diffuses through the stratum corneum the fastest, which is especially noticeable when comparing it to DEHP (Figure 4).

Acknowledgements/Disclaimer

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

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