INTRODUCTION TO THE MOBI SKIN PERMEATION MODEL

23RD APRIL 2021

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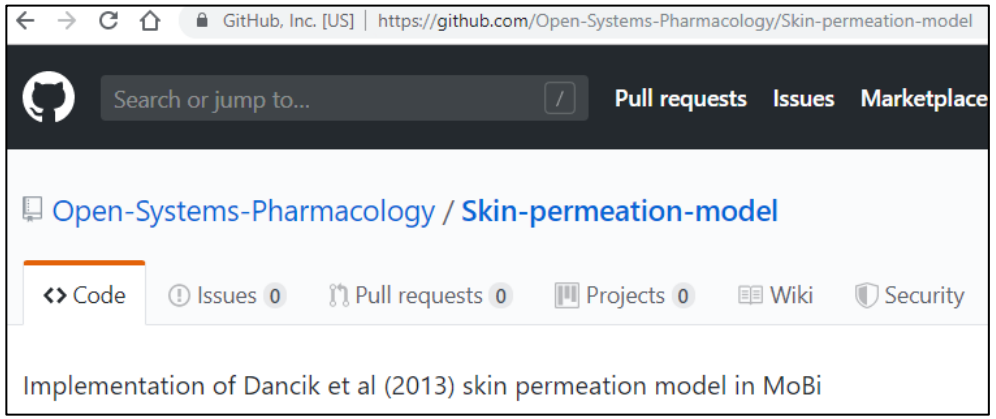
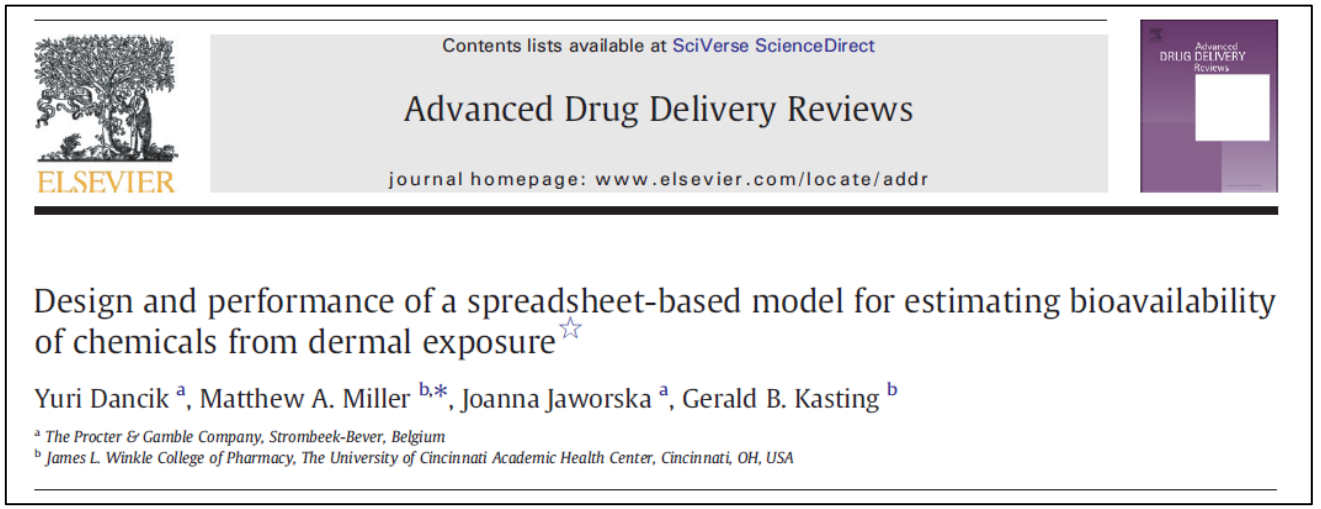
WHAT HAVE WE DONE AND WHY?

We have built a computational model of dermal absorption based on **Dancik et al. 2013**

- Model implemented in MoBi, available at **https://github.com/Open-Systems-Pharmacology/Skin-permeation-model**
- **Aim is to simulate disposition of dermally applied chemicals**
- Integrates many previously published 'sub-models'





SKIN ANATOMY

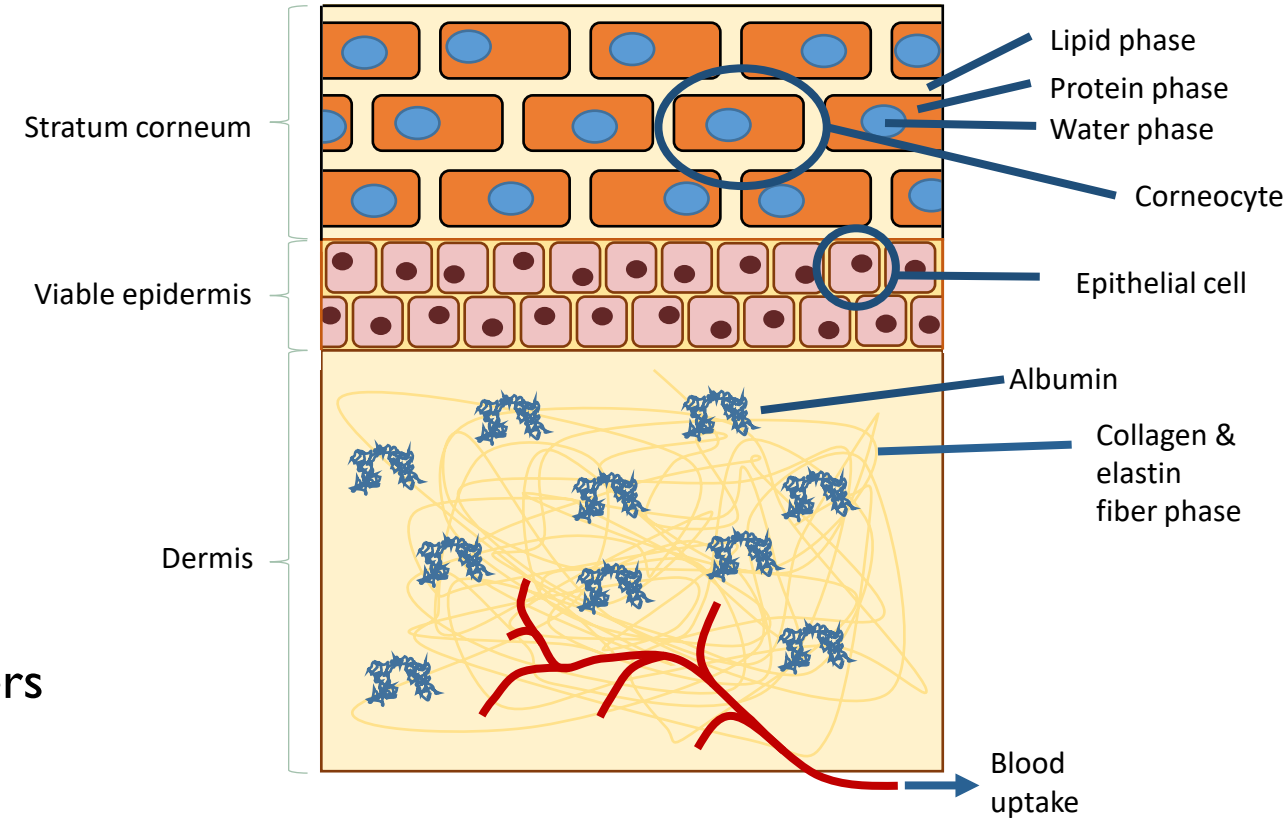
- Skin slab of cross-sectional area A

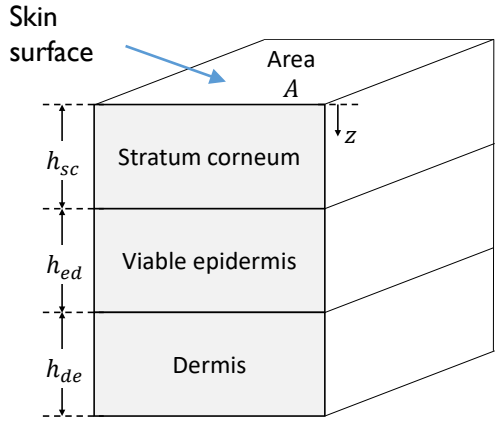
- Three stacked layers:
  - Stratum corneum (SC):
    - Lipid matrix (lipid phase)
    - Corneocytes (protein and water phases)
  - Viable epidermis (ED)
    - Epithelium
  - Dermis (DE):
    - Collagen & elastin fibers
    - Aqueous phase (partially albumin accessible)

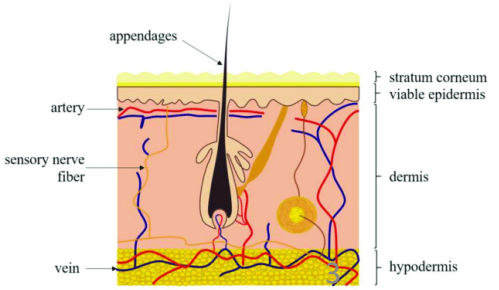
- Permeant applied on top of SC layer, diffuses into layers below

- *In vivo* clearance of the permeant takes place in the DE layer.

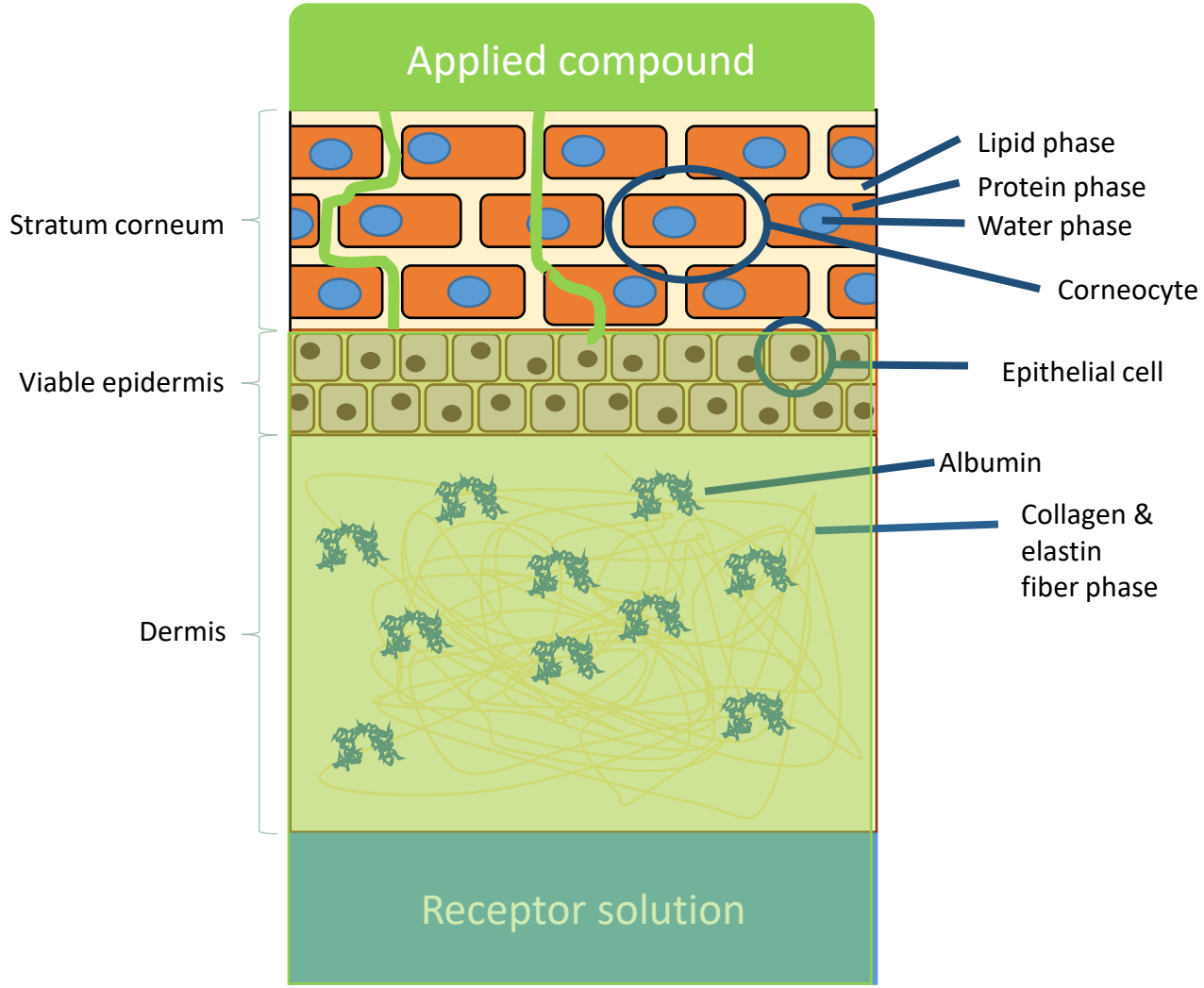
- Model allows for permeant evaporation from top layer







In vitro skin penetration



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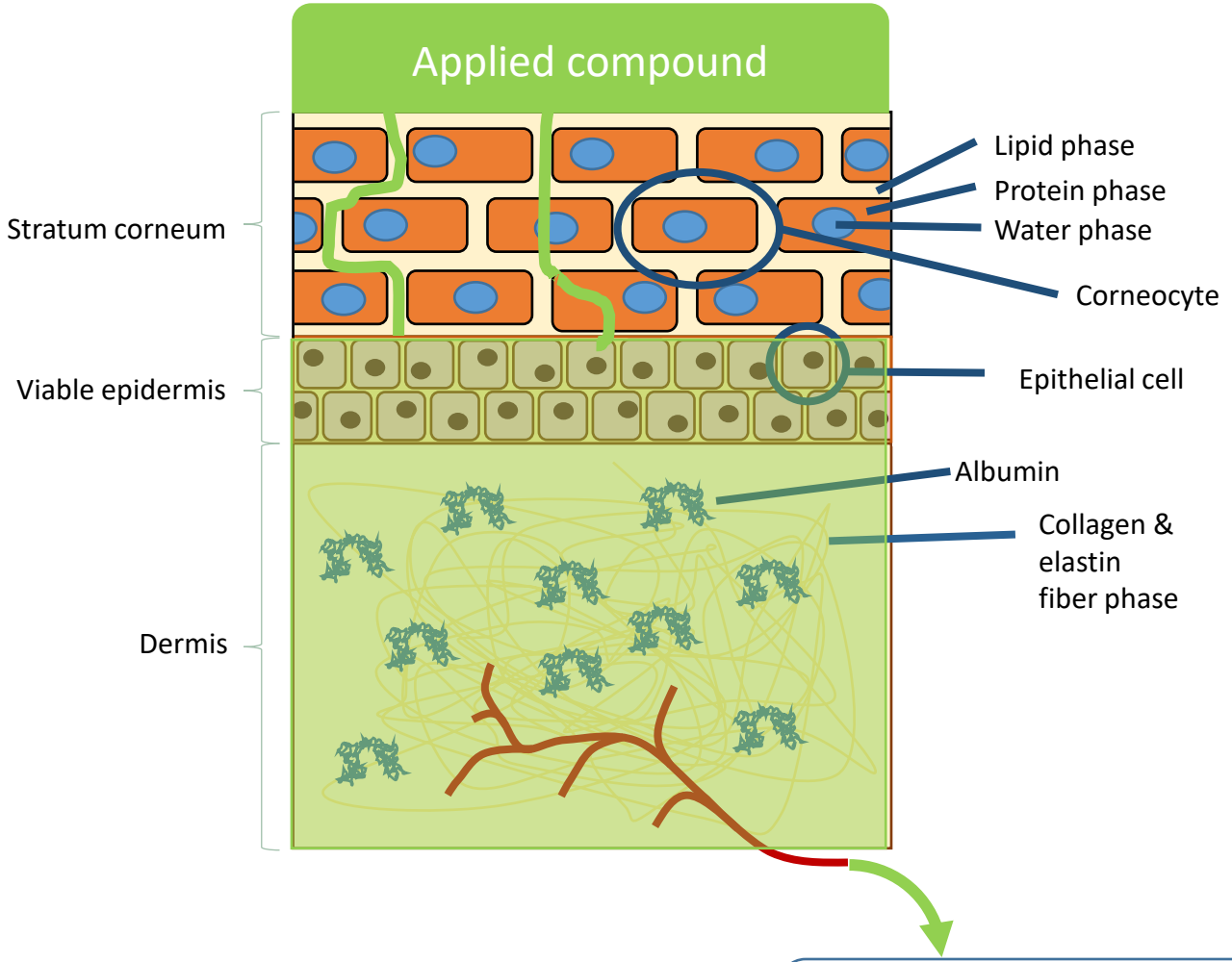


WHOLE-BODY
DISPOSITION MODEL

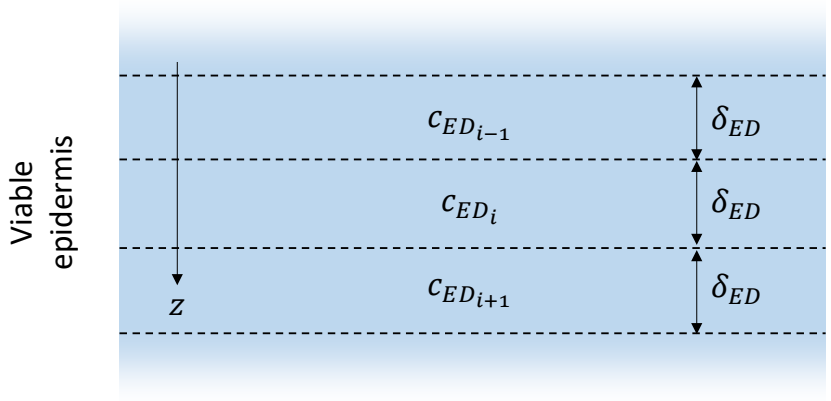
PK-Sim®

FLOW OF PERMEANT INTO SKIN GOVERNED BY THE DIFFUSION EQUATION

Diffusion of permeant numerically computed using method of finite differences and Fick's law:

$$J(z,t) = -D\frac{\partial c(z,t)}{\partial z}$$

J = diffusive flux, D = diffusion coefficient, c = local concentration of permeant



$$\frac{\partial c_{ED_i}}{\partial t} \approx \frac{1}{\delta_{ED}}\left(D_{ED}\cdot\frac{c_{ED_{i-1}}-c_{ED_i}}{\delta_{ED}} - D_{ED}\cdot\frac{c_{ED_i}-c_{ED_{i+1}}}{\delta_{ED}}\right) - f_m\left(c_{ED_i}\right)$$

$$f_m(c) = V_{max}\frac{c}{c+K_M}$$

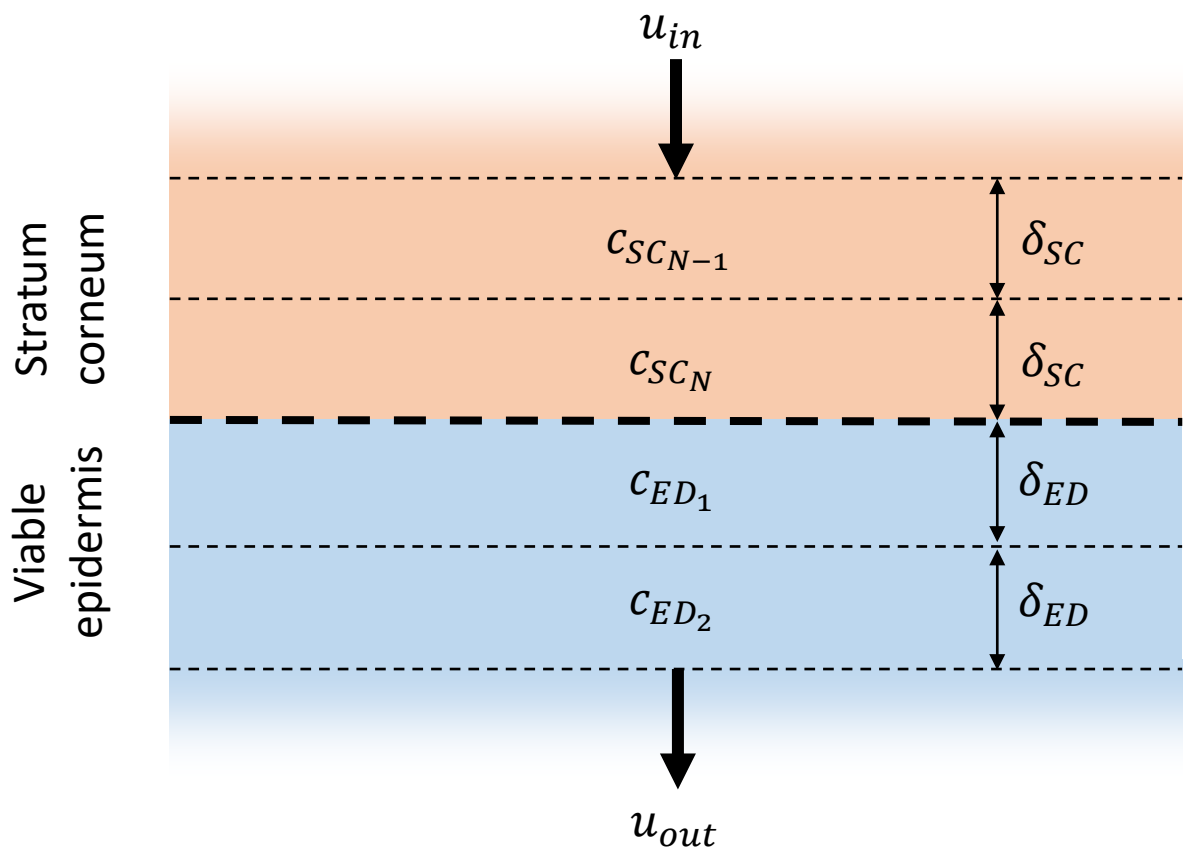
Permeant local concentration rate of change

Permeant flux in

Permeant flux out

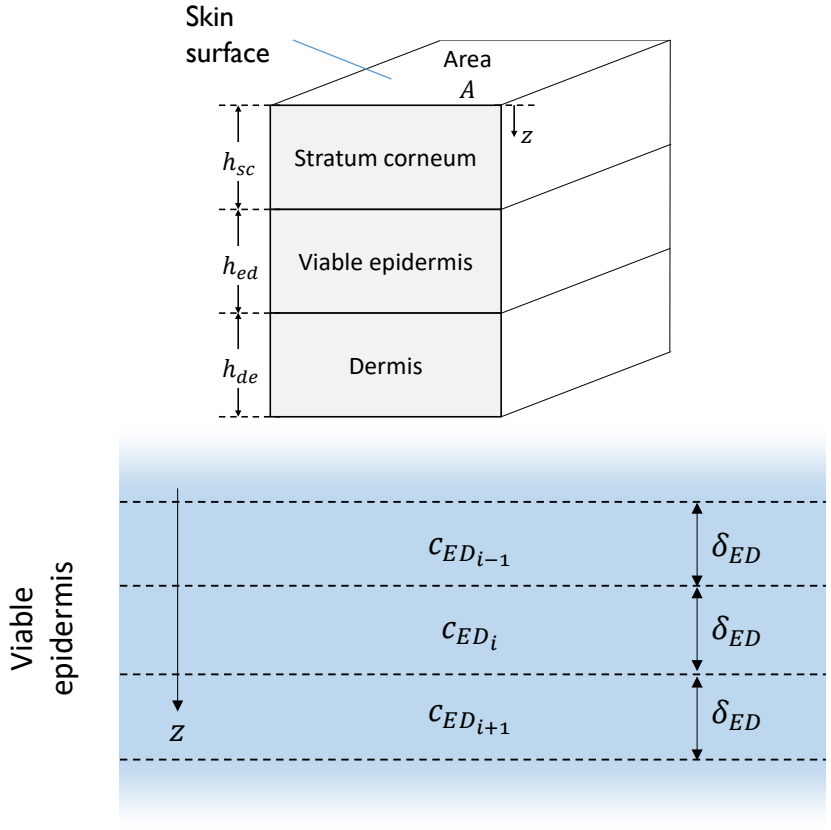
Permeant metabolism rate per unit volume

BOUNDARY CONDITIONS SUBLAYER INTERFACE: MASS BALANCE AND LOCAL EQUILIBRIUM



- Flow out of stratum corneum = flow into viable epidermis
- Ratio of concentrations at interface governed by partition coefficient between stratum corneum and viable epidermis

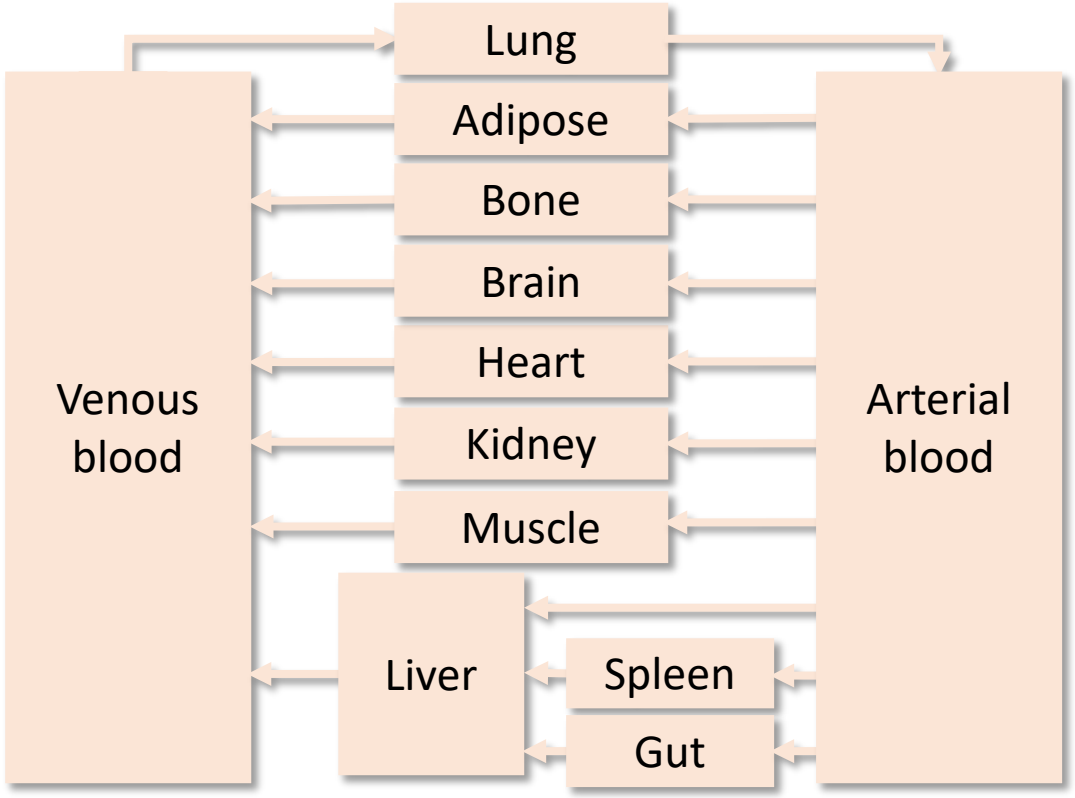
MODEL PHILOSOPHY: COMPARTMENTALIZE SKIN SUBLAYERS AS IN PBPK MODELS



Dermal model

SC, epidermis, dermis layers each compartmentalized into forty sublayers

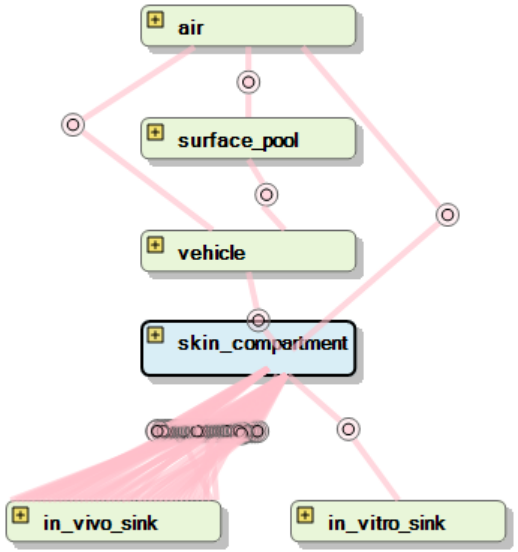
Permeant flows downwards from one layer to the next via diffusion.

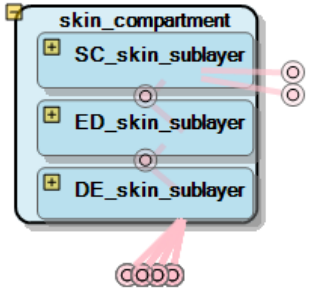


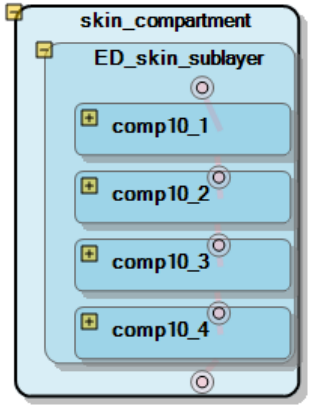
Typical PBPK model

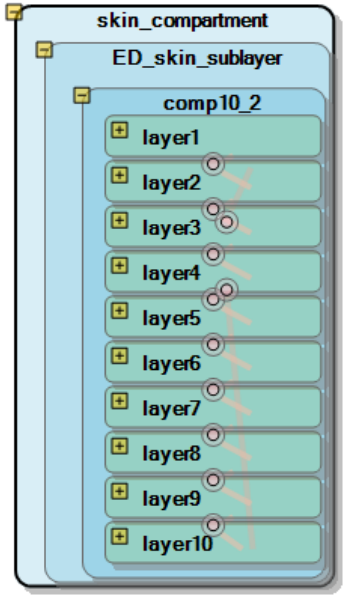
Blood flow transports drug

IMPLEMENTATION IN MOBI – A HIERARCHICAL VIEW OF MODEL STRUCTURE

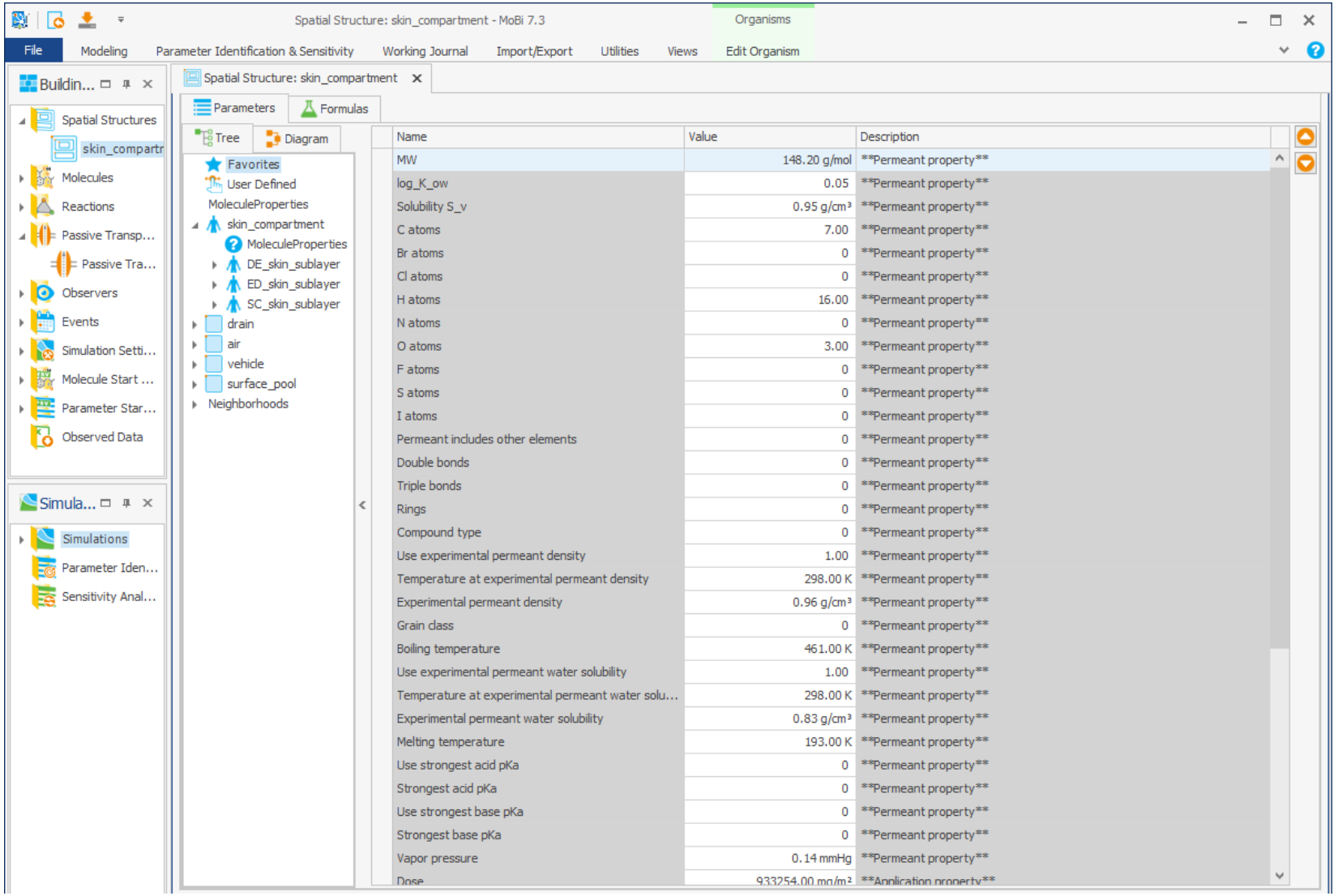


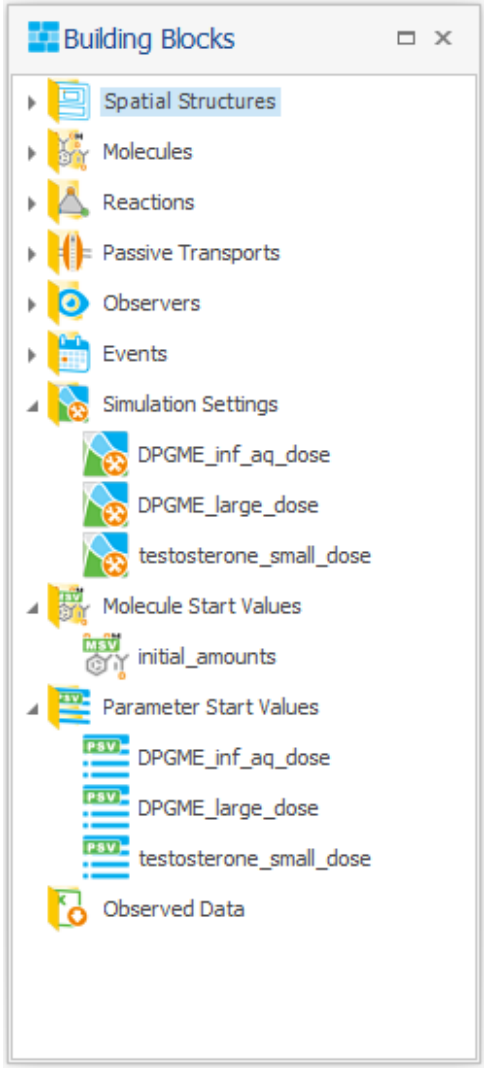




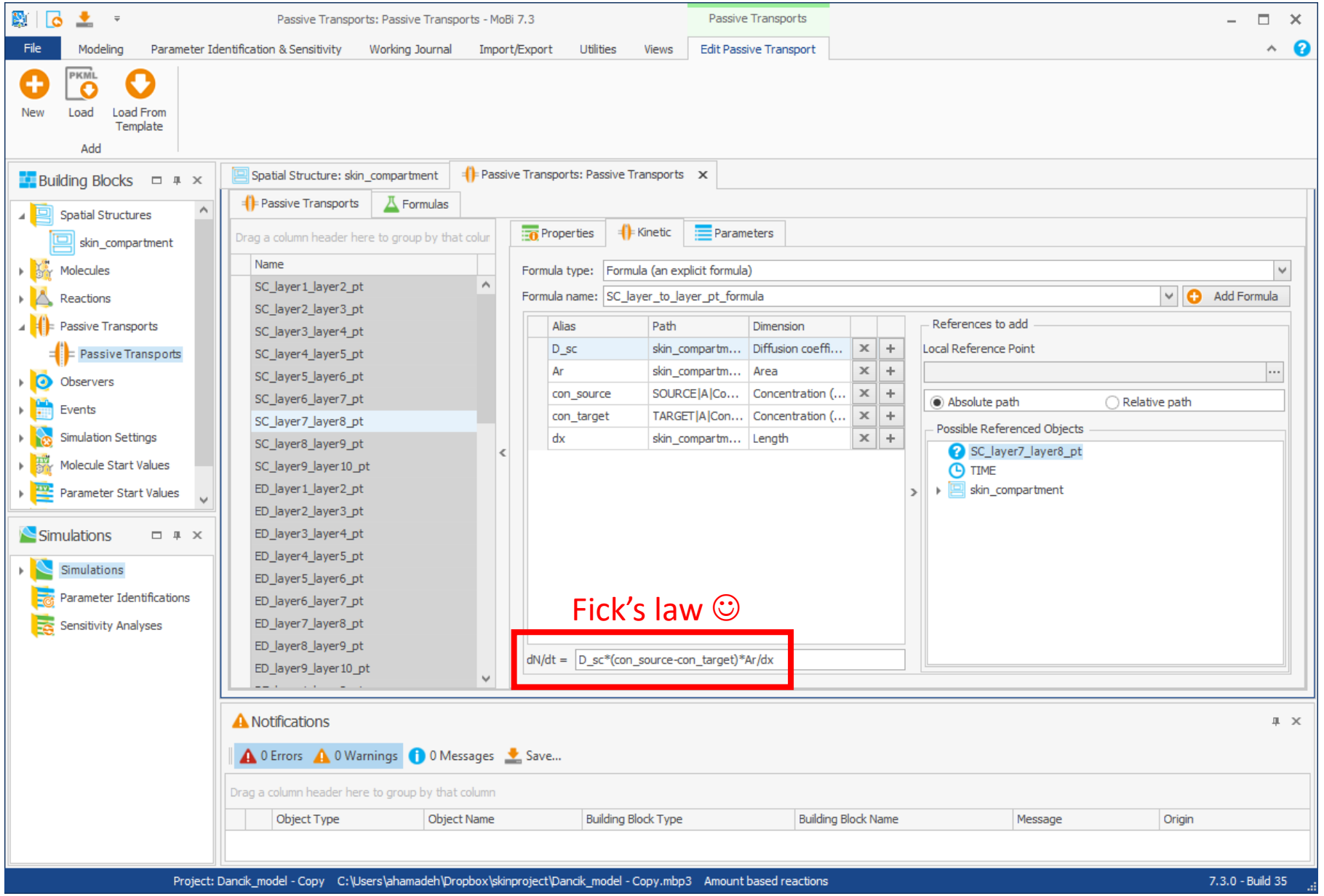


USER INPUTS FOR SIMULATION



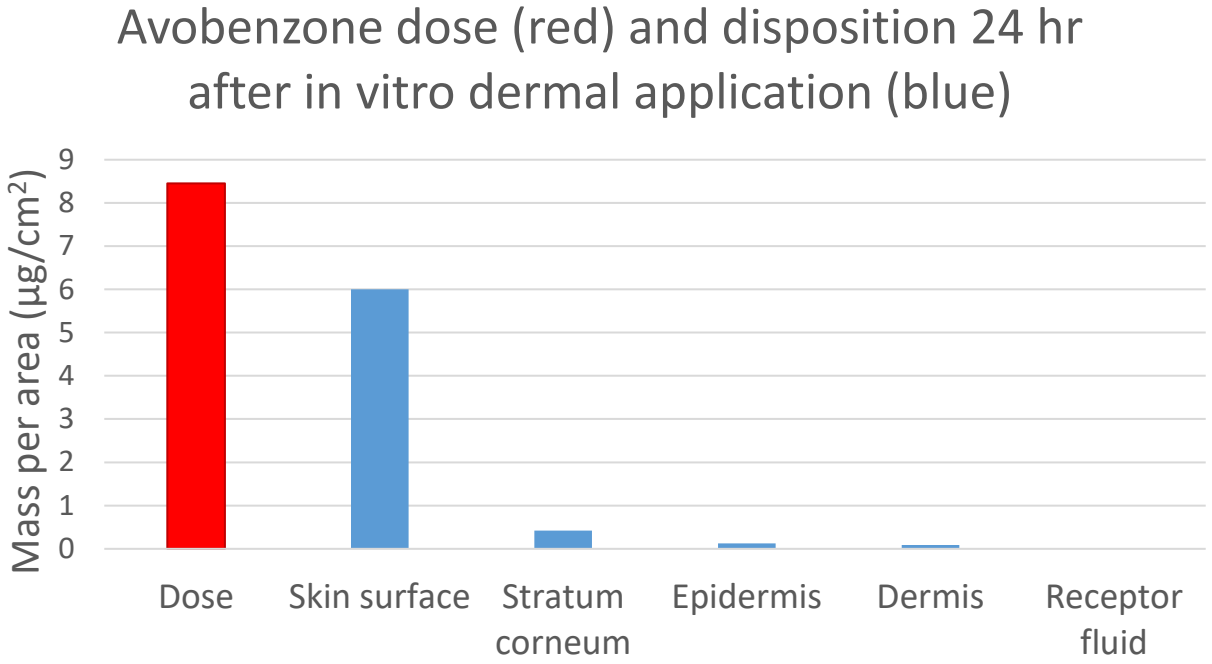


DIFFUSION COEFFICIENT USED IN IMPLEMENTATION OF FICK'S LAW



APPLIED EXAMPLE: IN VITRO-TO-IN VIVO EXTRAPOLATION OF UV FILTER SKIN ABSORPTION

- **In vitro skin penetration experiment:**
  - **Avobenzone** in vitro skin penetration data provided by **A. Najjar & D. Lange, Beiersdorf.**
  - Measured accumulation of avobenzone in skin layers and receptor fluid over 24 hrs
  - Dose: 8.45µg/cm^2
  - Solvent: Ethanol



- **Want to:**
  - **learn model parameters from data**
  - **estimate in vivo dermal absorption based on learned parameters**

- **Sensitivity analysis shows dermal absorption sensitive to some uncertain model parameters (to be optimized):**
  - Avobenzone lipophilicity (Range: 4.2-6.1)
  - Water solubility (Range: 10^{-8} – 10^{-6} g/cm^3)
  - Permeability across stratum corneum lipids (Range: $10^{-7.5}$ – 10^{-5} cm/s)

FINAL REMARKS

- Presented a MoBi implementation of the Dancik et al. 2013 dermal absorption model

- MoBi simulates skin penetration by solving diffusion equation
  - anatomical skin layers are divided into thin sub-layers (compartments)
  - Fick's law applied to model diffusive flow between sub-layers

- MoBi model can be appended to a whole-body model in PK-Sim

- Presented an example of dermal model optimization to in vitro data for extrapolation to in vivo scenario

- We have built a **dedicated R package** based on **OSPSuite-R** for MCMC-based **in vitro to in vivo inference of dermal absorption**

- Please send any questions to **ahamadeh@uwaterloo.ca**

Funding for the work presented here was made possible, in part, by the Food and Drug Administration through grant U01FD006549. This work reflects the views of the authors and should not be construed to represent FDA's views or policies. Views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organizations imply endorsement by the United States Government. Parts of the herein presented work are supported by Procter & Gamble.