A WORKFLOW FOR MECHANISTIC DERMAL MODEL OPTIMIZATION AND IN VITRO-IN VIVO INFERENCE

23RD JULY 2020

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

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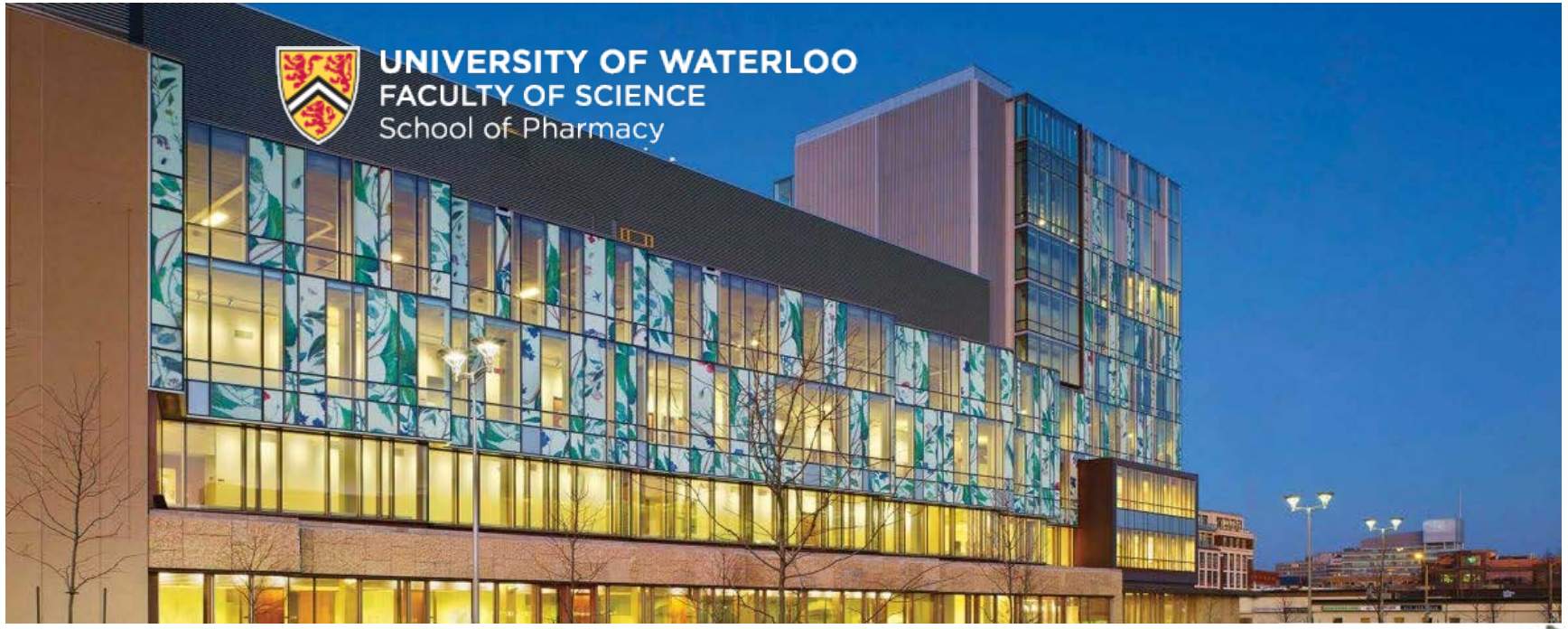
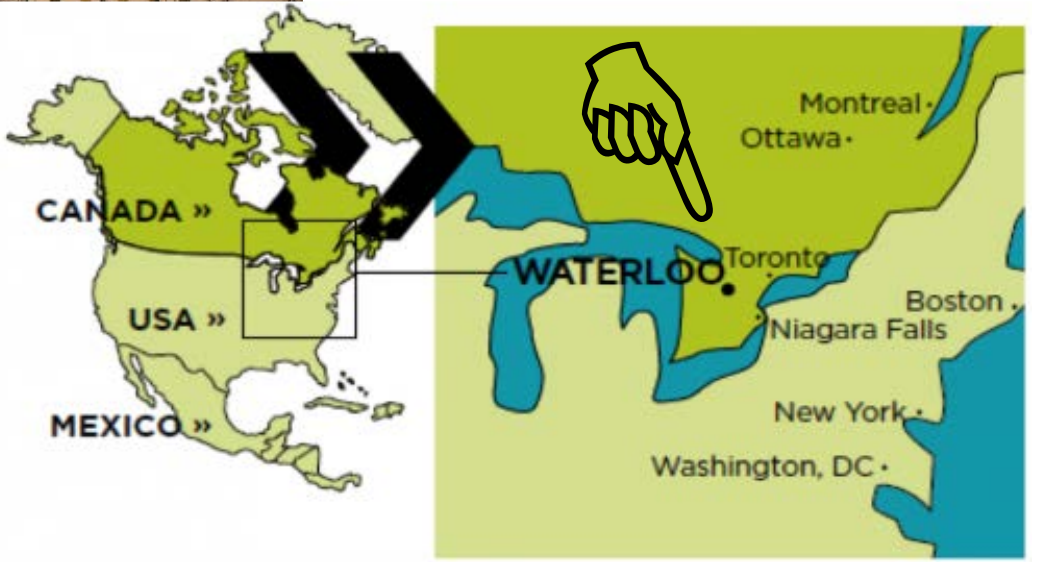
INTRODUCTIONS



We're @ the black dot



About me:

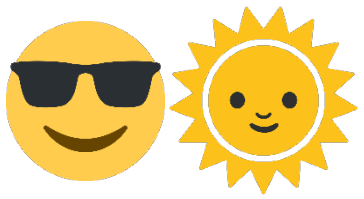
- PhD in control systems engineering (Cambridge)
- Postdoc in systems & synthetic biology (MIT)
- Approach dermal absorption from a mathematical modeling & optimization POV ☺

AIM: EXTRACT MECHANISTIC INFORMATION FROM IN VITRO DATA, USE INFORMATION FOR IN VIVO PREDICTIONS

- ***Present our Open Systems Pharmacology implementation of the Kasting (mechanistic) skin penetration model***
  - Enables the assessment of whole-body disposition of dermally applied compounds

- ***Assess the predictive ability of the Kasting model using recent in vitro data***

- ***Present a workflow to leverage in vitro information for prediction of in vivo skin penetration under various exposure scenarios***
  - ***Examples:*** *cosmetics, pharmaceuticals and a sunscreen*



Open Systems Pharmacology Suite implementation of the Kasting skin penetration model

PK-Sim

- Whole-body PBPK modeling and optimization software.
- Simulates whole body responses at both the individual and population level.

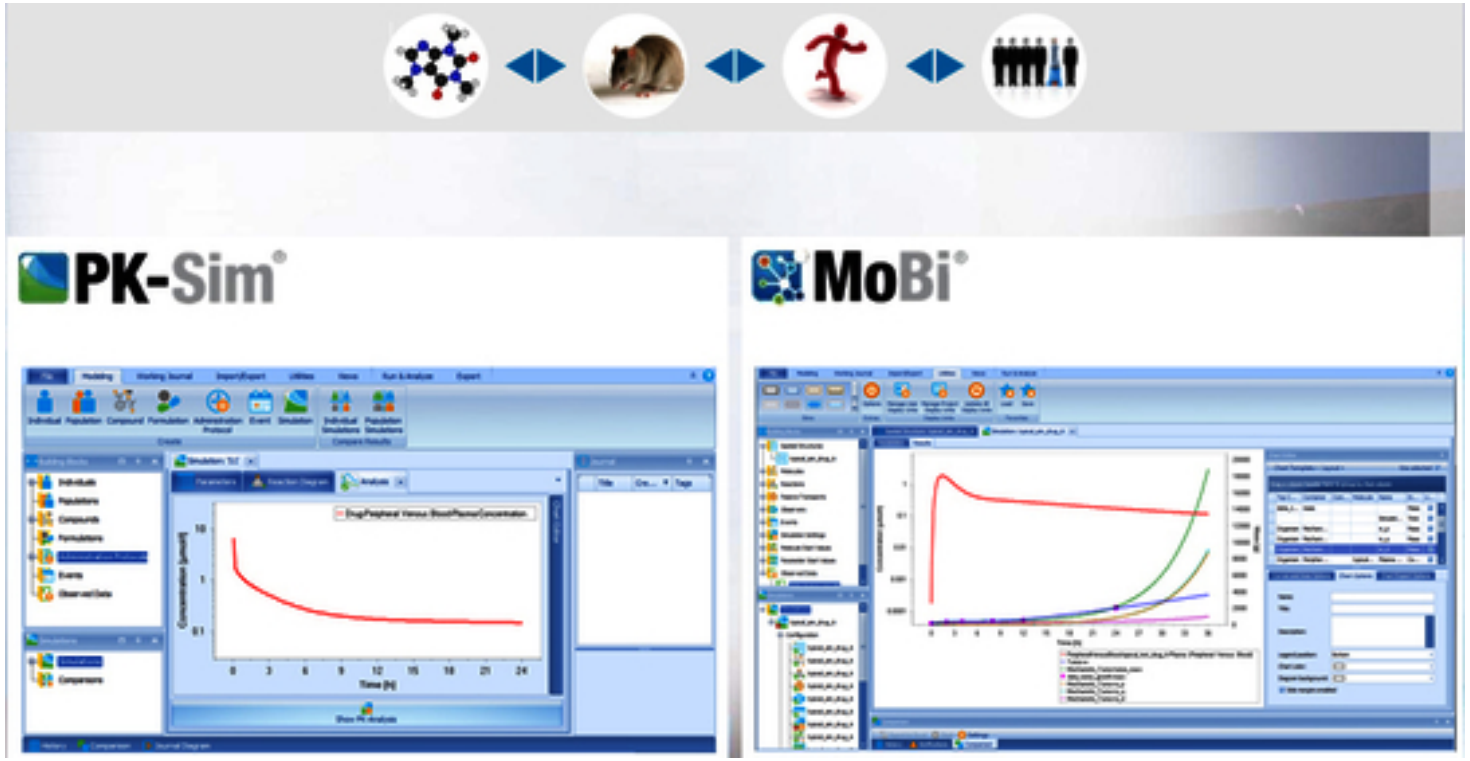
MoBi

- Software for building custom compartmental models that can be appended to PKSim whole-body models.

OSPSuite-R

- R interface to PK-Sim and MoBi models.

http://www.open-systems-pharmacology.org/



OPEN SYSTEMS PHARMACOLOGY

THE KASTING (MECHANISTIC) MODEL OF SKIN PENETRATION, IMPLEMENTED IN MOBI

Contents lists available at SciVerse ScienceDirect

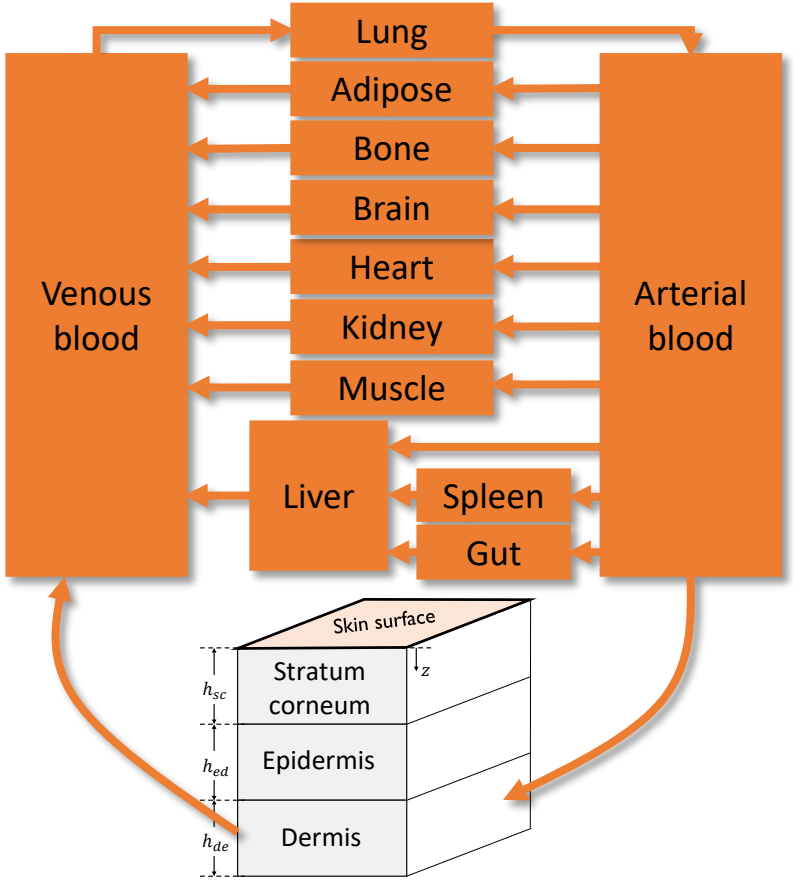
Advanced Drug Delivery Reviews

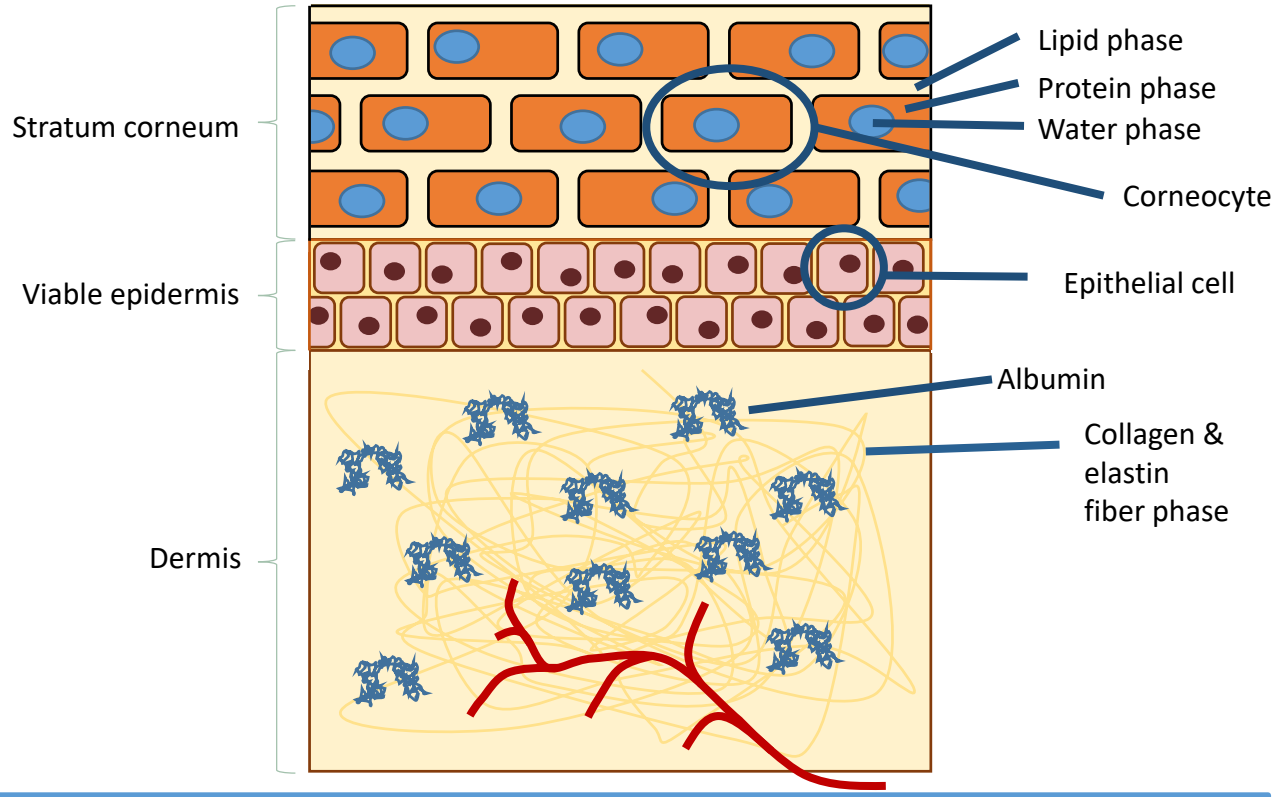
journal homepage: www.elsevier.com/locate/addr

Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure ☆

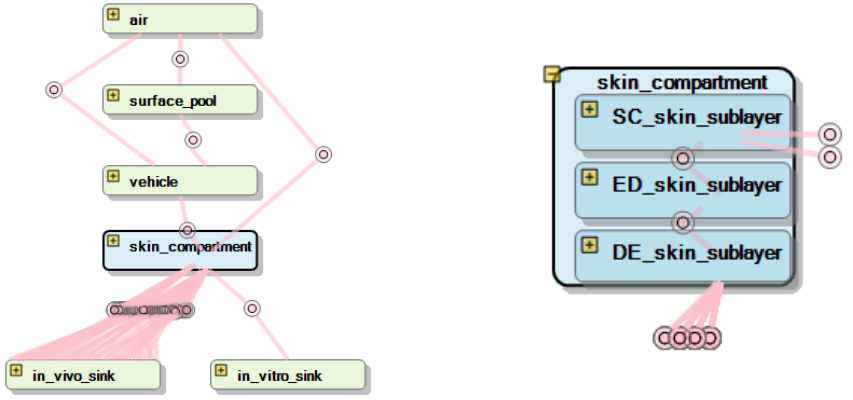
Yuri Dancik [a], Matthew A. Miller [b,*], Joanna Jaworska [a], Gerald B. Kasting [b]

[a] The Procter & Gamble Company, Strombeek-Bever, Belgium
[b] James L. Winkle College of Pharmacy, The University of Cincinnati Academic Health Center, Cincinnati, OH, USA





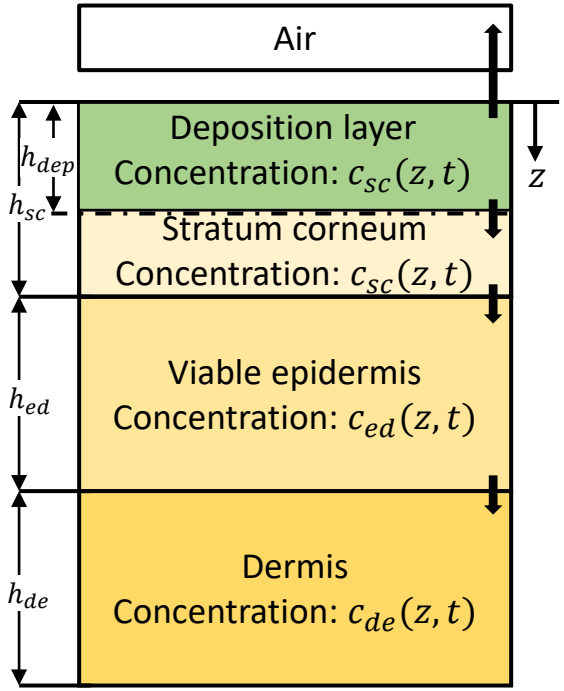
https://github.com/Open-Systems-Pharmacology/Skin-permeation-model



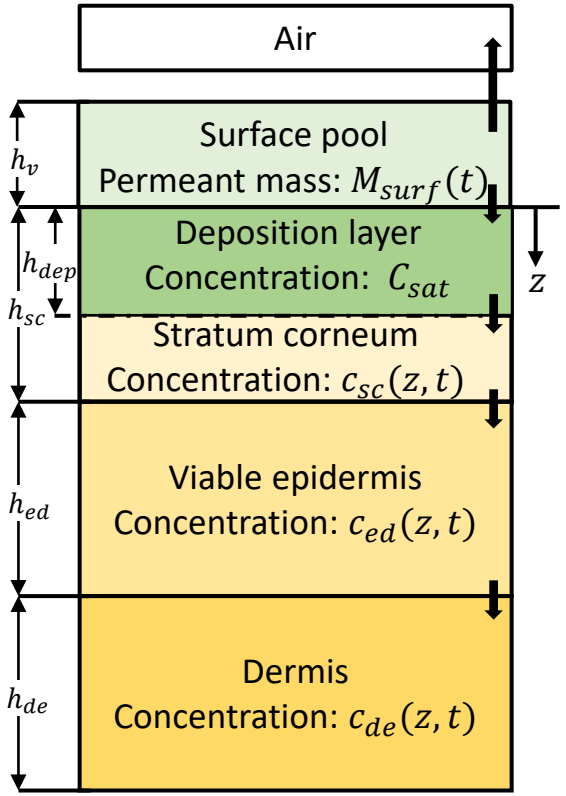
MODEL CAN CAPTURE VARIOUS APPLICATION SCENARIOS

Volatile/no vehicle case

Case 1
Non-saturating dose

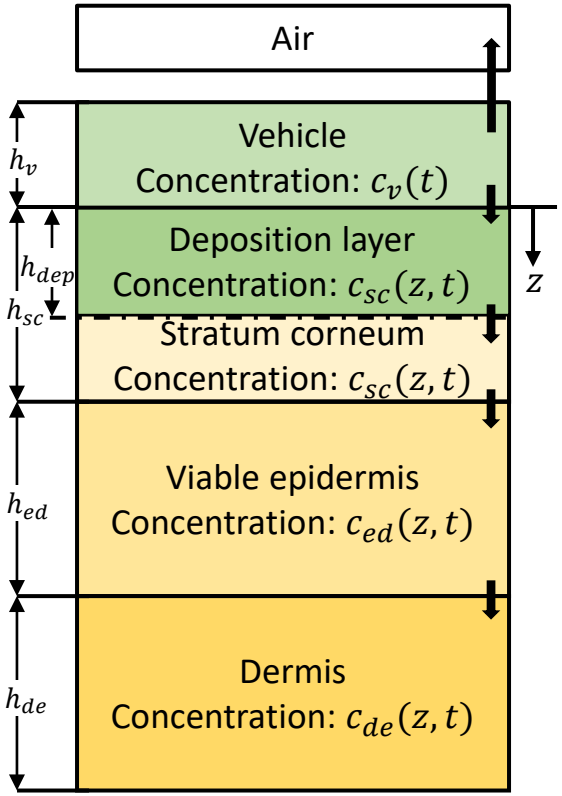


Case 2
Saturating dose

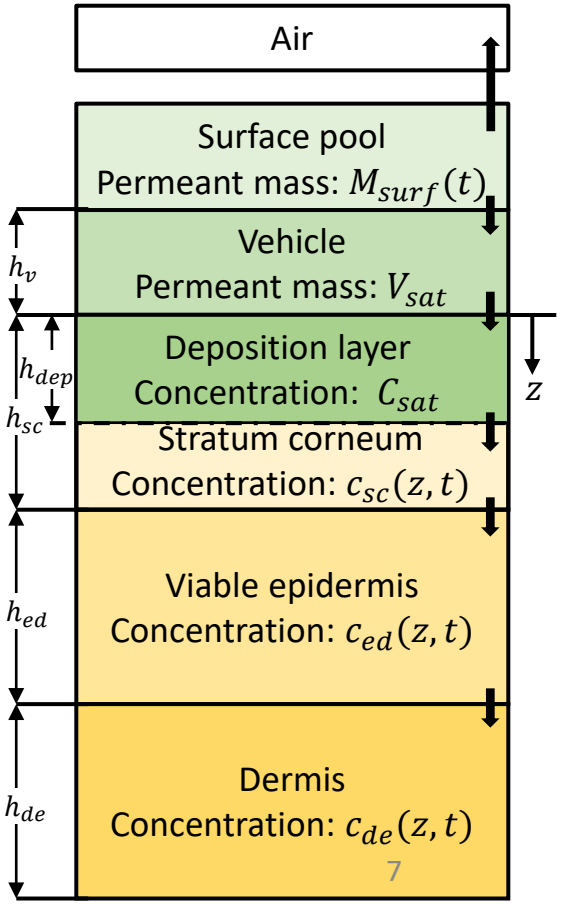


Immobile vehicle case

Case 3
Non-saturating dose

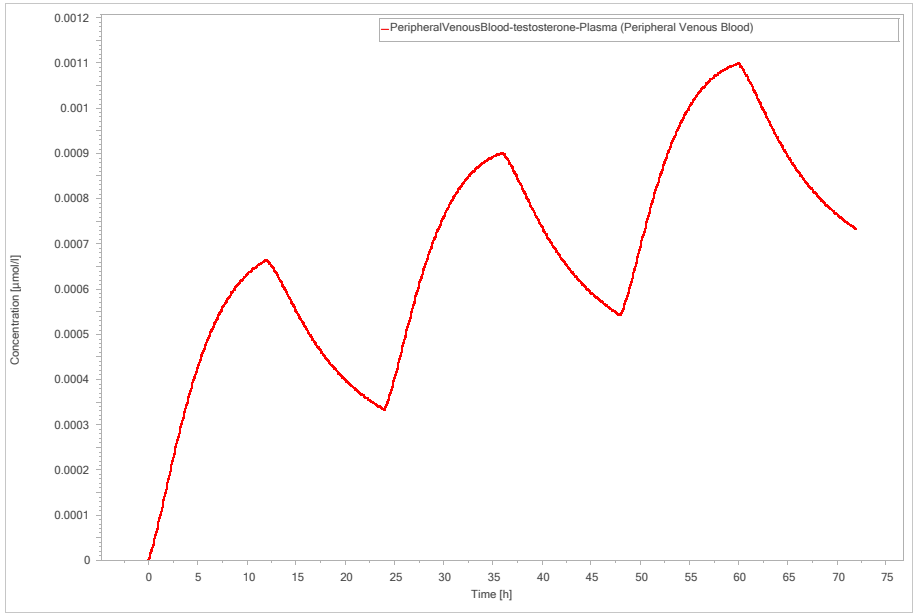


Case 4
Saturating dose



FEATURES OF THE OPEN SYSTEMS PHARMACOLOGY SKIN MODEL IMPLEMENTATION

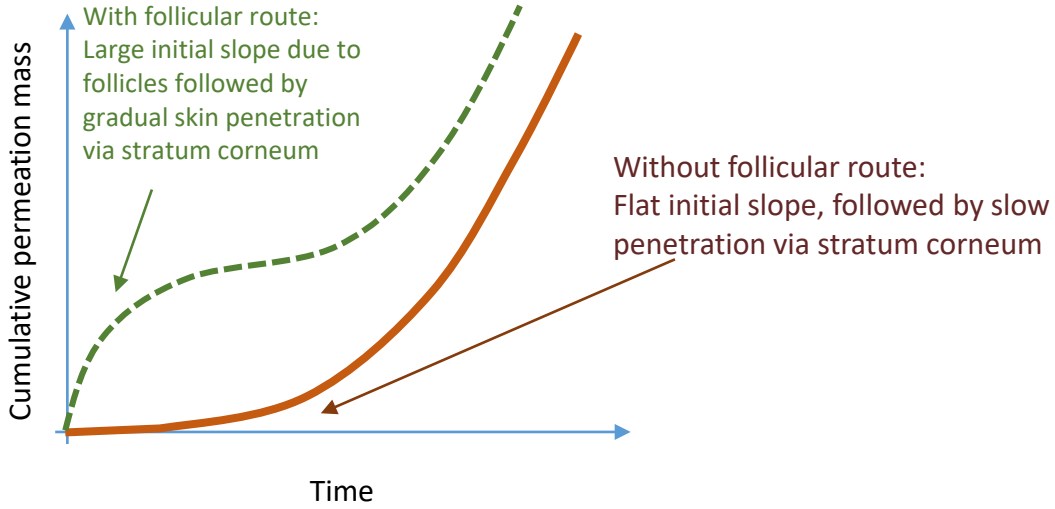
Multiple dosing



PK-Sim whole body model + dermal model simulation
500µg/cm^2 of testosterone applied to 100cm^2 of skin once every 24 hours over a period of 72 hours.
The testosterone is removed from the skin surface 12 hours after every application.

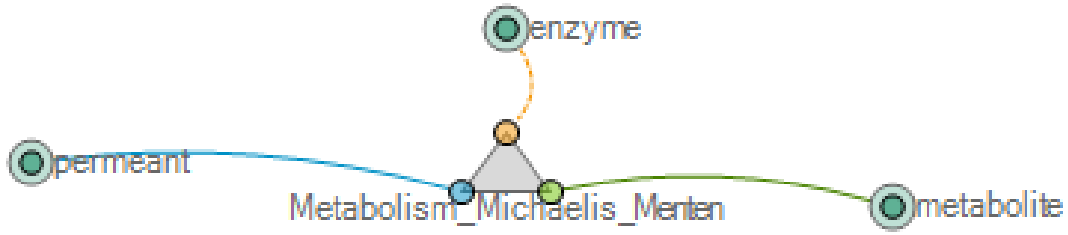
Follicle compartment

Follicles can bypass stratum corneum and create a ‘fast’ route for the permeant to reach dermis.



Skin penetration via follicle route modeled as first order process

Metabolism in epidermis/dermis



Assessment of the predictive ability of the Kasting model

HEWITT ET AL., 2019: RECENT IN VITRO SKIN PENETRATION EXPERIMENTS

- 56 compounds tested in vitro
- Each experiment repeated on three non-occluded skin sections of four individuals.
- Paper reports kinetic receptor fluid data and amounts in SC, epidermis & dermis at end of experiment.
- Paper lists in vivo measures from the literature for 7 compounds.

RESEARCH ARTICLE

Journal of Applied Toxicology WILEY

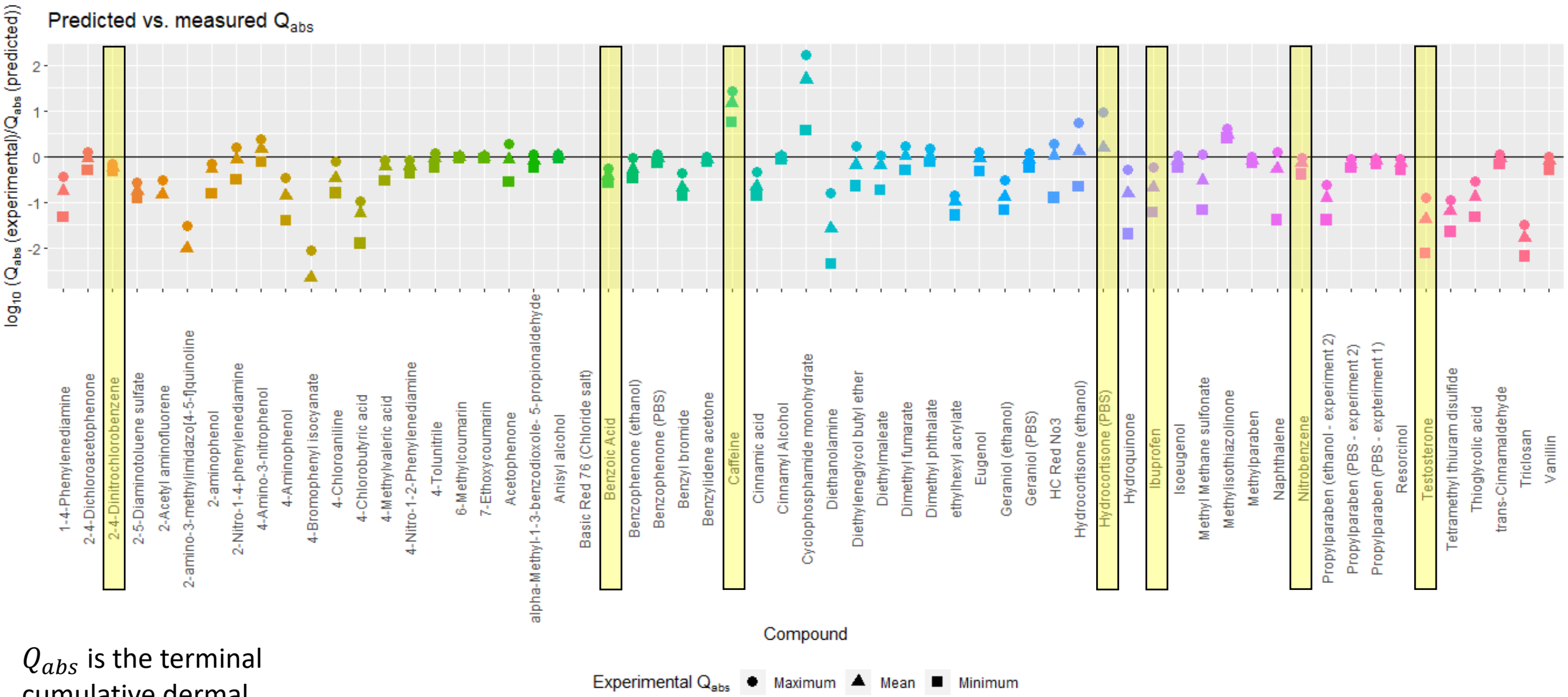
Measurement of the penetration of 56 cosmetic relevant chemicals into and through human skin using a standardized protocol

Nicola J. Hewitt[1] | Sébastien Grégoire[2] | Richard Cubberley[3] | Hélène Duplan[4] | Joan Eilstein[2] | Corie Ellison[5] | Cathy Lester[5] | Eric Fabian[6] | Julien Fernandez[7] | Camille Géniès[4] | Carine Jacques-Jamin[4] | Martina Klaric[1] | Helga Rothe[8] | Ian Sorrell[3] | Daniela Lange[9] | Andreas Schepky[9]

ASSESSMENT OF UNOPTIMIZED KASTING MODEL USING *IN VITRO* DATA FROM HEWITT ET AL.

- Our MoBi implementation of Kasting model was simulated for the 56 compounds tested in Hewitt et al. under *in vitro* simulation conditions
- In vitro mass balance was preserved in simulations through the adjustment of evaporation rate of each compound
- Simulations were compared to *in vitro* cumulative dermal absorption (Q_{abs}) at 24 hours from Hewitt et al.

IN VITRO ASSESSMENT OF KASTING MODEL: THE MODEL MOSTLY OVERPREDICTS CUMULATIVE ABSORPTION



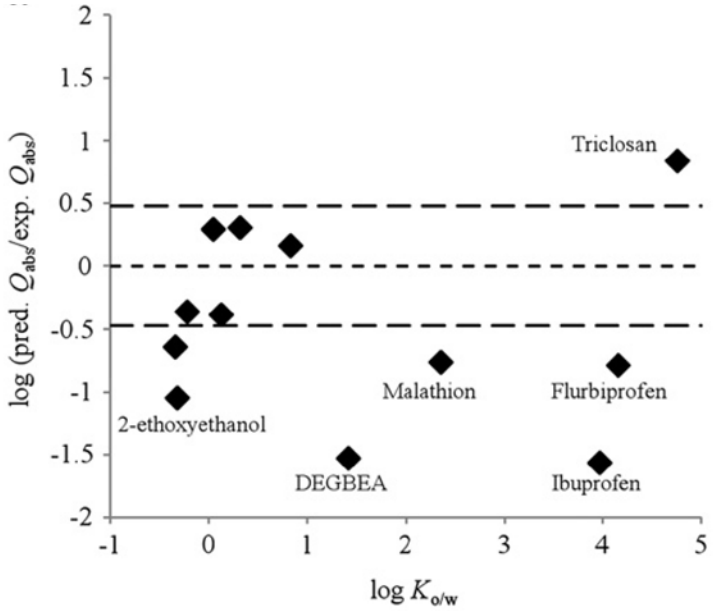
Q_{abs} is the terminal cumulative dermal absorption after 24 hours.

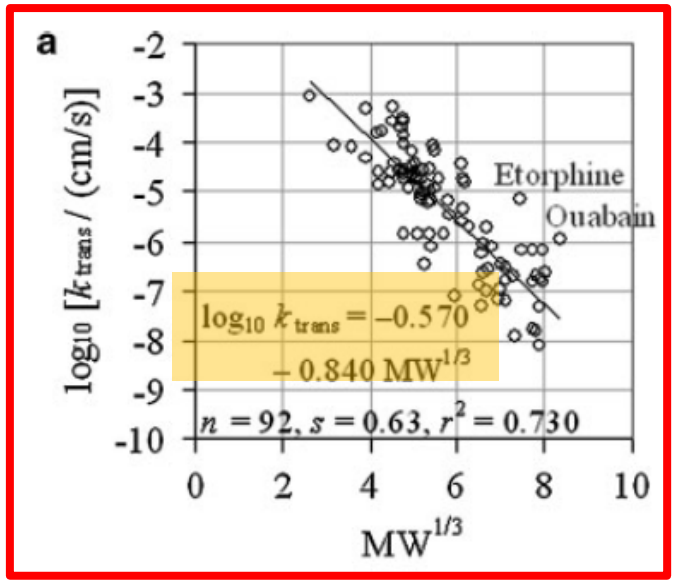
A workflow to leverage in vitro information for prediction of in vivo skin penetration under various exposure scenarios

PUBLISHED MODEL HAS VARIABLE PREDICTIVE PERFORMANCE

Several **uncertain** parameters **strongly impact** skin penetration. Eg:

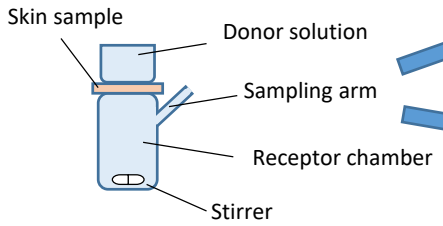
- stratum corneum thickness
- permeability of lipid bilayers
- lipid/water partition coefficient
- protein water partition coefficient





VISION: MODEL OPTIMIZATION SHOULD FOLLOW A STANDARD WORKFLOW

In vitro skin permeation test data



Testing data

Training data

Model testing

Model optimization

Model modification to *in vivo* scenario

Prediction of *in vivo* permeation

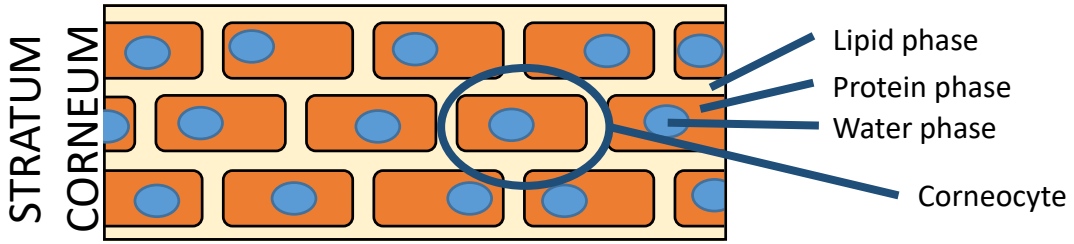
Model parameters for optimization

- Skin properties
- Experimental conditions
- Permeant properties
- Dose

Initial model construction *in silico*

- Sensitivity analysis
- Uncertainty analysis

- ***Given in vitro skin penetration data for <u>a single compound</u>:*** learn likely values of 'important' parameters for that compound.
  - *lipid bilayer permeability,*
  - *lipid/water partition coefficient*
  - *protein/water partition coefficients*



- 'Important' parameters:
  - have a large impact on skin penetration model predictions,
  - are uncertain

- *Model parameters can be classified as:*
  - Compound-specific parameters (common to all individuals) eg lipid/water partition coefficients
  - Individual-specific parameters, eg stratum corneum thickness

MODEL OPTIMIZATION STRATEGY

Step A: Employ a **Hierarchical Monte Carlo** optimization algorithm (Metropolis-Hastings) to narrow down model parameter values in the form of a **joint probability distribution** for all parameters **(ie maintaining correlations between optimized parameters)**

Algorithm traverses parameter space and either accepts or rejects parameter values into joint probability distribution depending on the **simultaneous fit** of **all** individuals' simulated dermal absorption to their respective **in vitro** measurements

Algorithm iterates between testing

- compound-specific parameters common to all individuals
- individual-specific parameters

Step B: Marginalize joint distribution to obtain distributions for **compound-specific parameters only**.

Step C: Simulate **in vivo** model using samples from compound-specific parameters' joint probability distribution obtained in **Step B**, with individual-specific parameters set to mean literature-derived values.

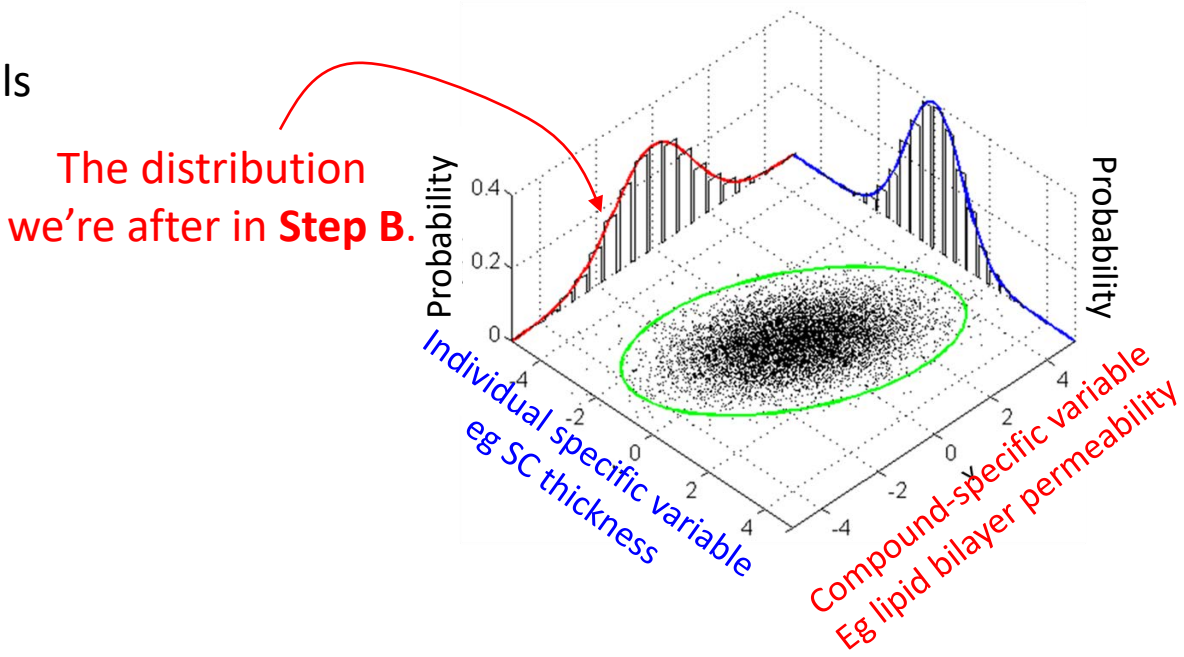


Image adapted from Wikipedia

WORKFLOW STEPS: IN VITRO TO IN VIVO INFERENCE

- **Step 1:** Identify parameters that are uncertain and that strongly impact model estimates of in vitro skin penetration.

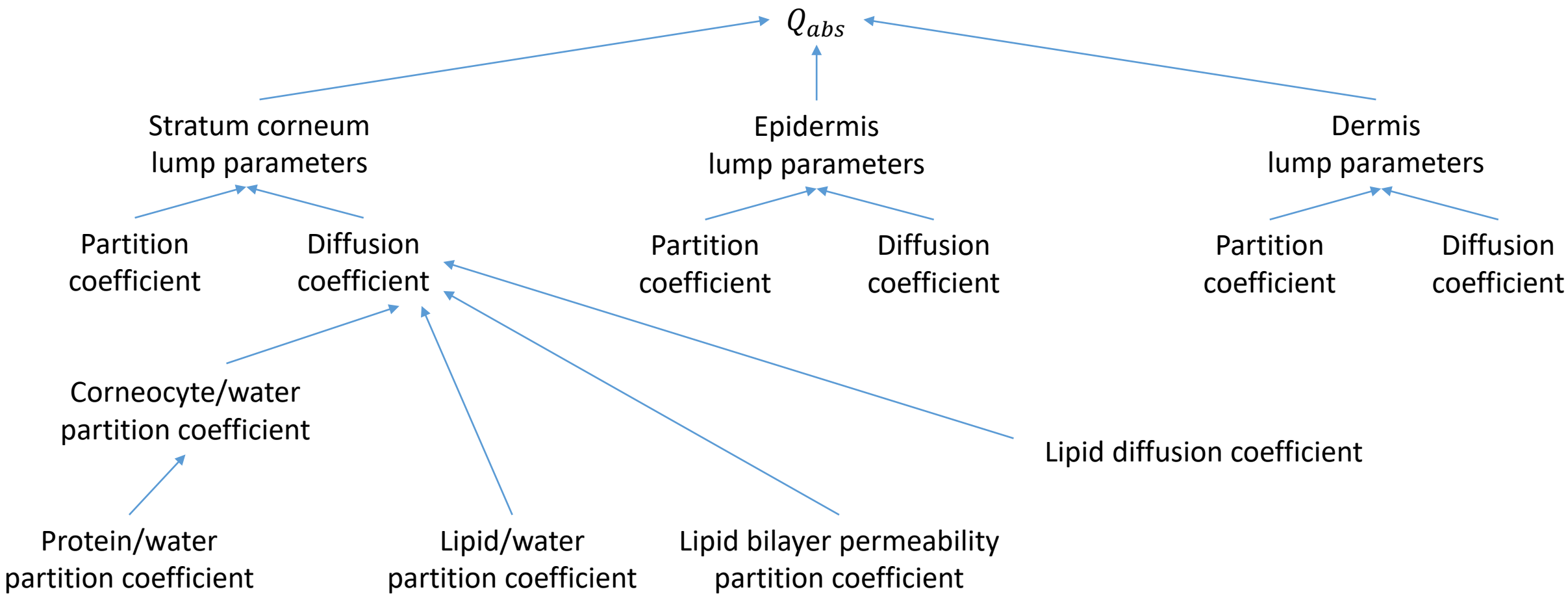
- **Step 2:** Identify the joint posterior probability distribution of these parameters given in vitro skin penetration observations

- **Step 3:** Verify success of model fit to observed in vitro data using visual predictive checks:
  - Samples of the full set of optimization parameters repeatedly drawn from the compound's joint posterior distribution.
  - Each sample is input into the model.
  - The in vitro model is simulated for each sample.

- **Step 4:** Model estimates of cumulative dermal absorption in vivo then tested against *in vivo* data.

Examples: cosmetics, pharmaceuticals and a sunscreen

PARAMETERS ASSESSED IN SENSITIVITY ANALYSIS



UNCERTAIN AND SENSITIVE MODEL PARAMETERS TO BE OPTIMIZED

Compound-specific parameters found to be both uncertain and sensitive:

- *lipid bilayer permeability (k_{trans}),*
- *lipid/water partition coefficient ($K_{lip/w}$)*
- *protein/water partition coefficients ($PC_{pro/water}$)*

Parameter (units)	Nominal value (Uncertainty range)
$\log_{10} k_{trans}$ (cm/s)	Nominal value = $0.570 - 0.840MW^{\frac{1}{3}}$ Uncertainty range = Nominal value ± 1.26
$\log_{10} PC_{pro/water}$	Nominal value $= 0.27 \log_{10} K_{o/w} + \log_{10} 5.4$ Uncertainty range = Nominal value ± 0.32
$\log_{10} K_{lip/w}$	Nominal value $= 0.81 \log_{10} K_{o/w} + \log_{10} 0.43$ Uncertainty range = Nominal value ± 0.434

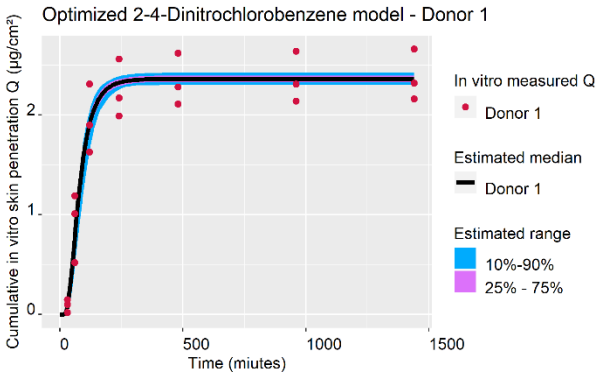
Uncertain and sensitive individual-specific parameters:

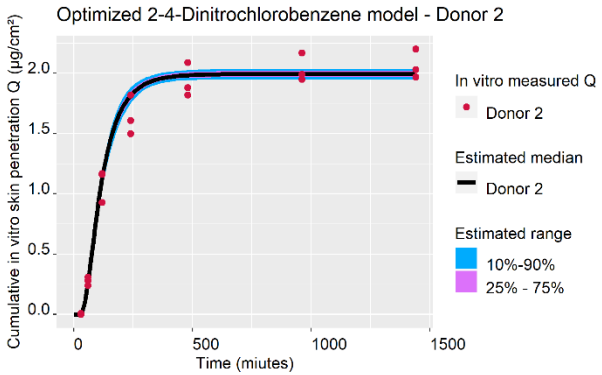
- *Stratum corneum thickness (10-40 um)*
- *Stratum corneum water mass:dry mass ratio (0.43-2.75)*

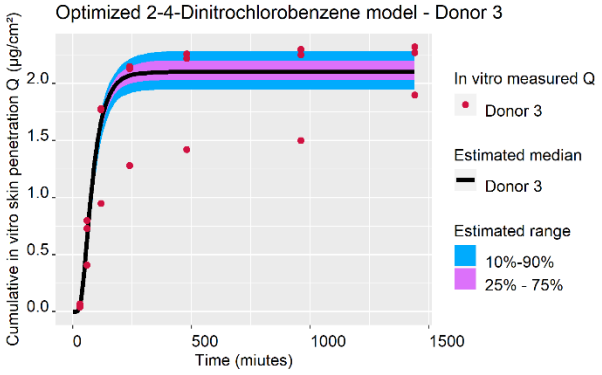
MODEL OPTIMIZATION RESULTS: 2,4-DINITROCHLOROBENZENE

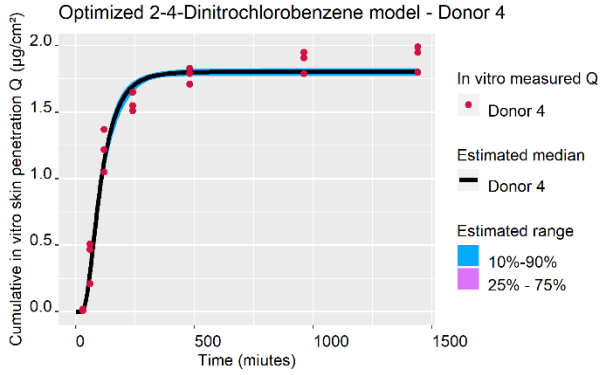
In vitro experiment (Hewitt et al., 2019):

- Dose applied: 4.26 µg/cm^2
- 24 hour, non-occluded experiment
- Solvent: phosphate-buffered saline (PBS)







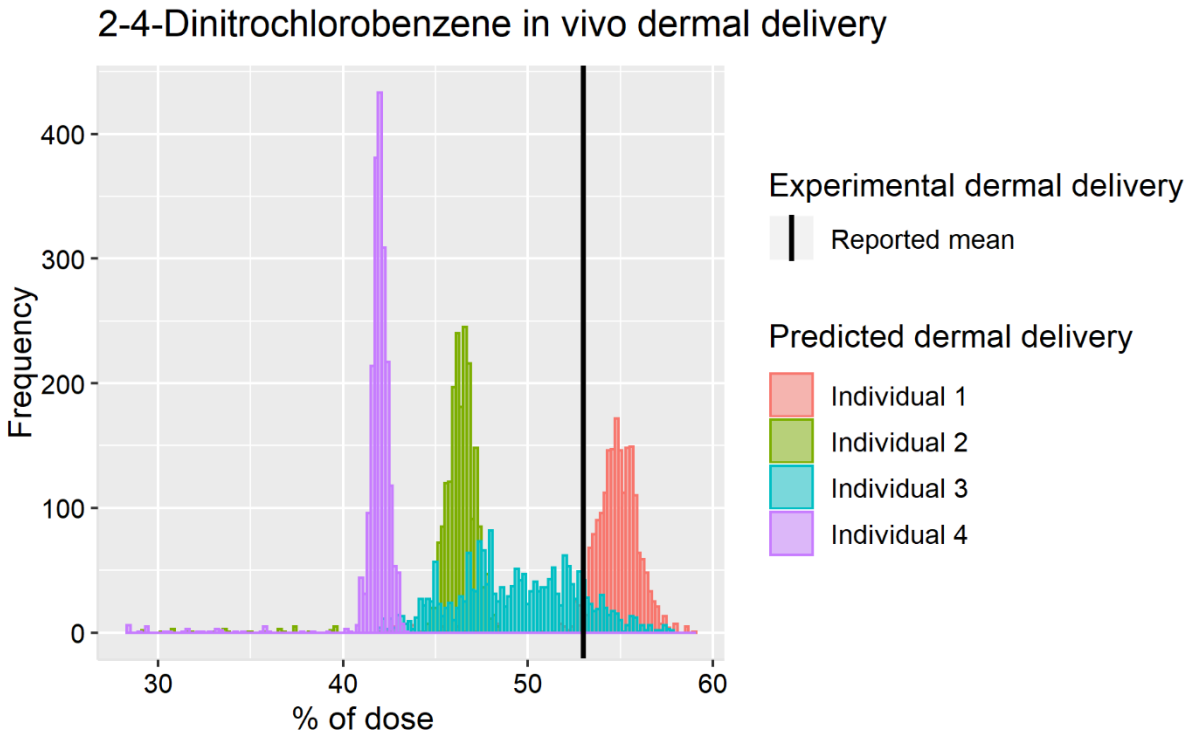


- Algorithm fitted model to cumulative mass of permeant in receptor fluid (Q)
- Both kinetics and terminal cumulative mass in receptor fluid fitted very well.

PREDICTION OF IN VIVO ABSORPTION: 2,4-DINITROCHLOROBENZENE

In vivo experiment (Feldmann and Maibach,1970):

- Dose: 4 µg/cm^2
- 5–day, non-occluded experiment
- Solvent: Acetone (volatile)

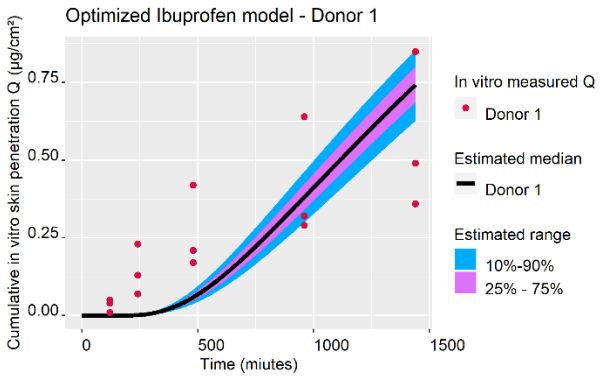


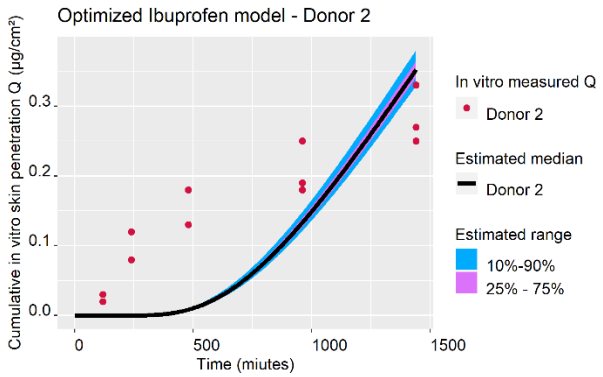
- Repeatedly sampled parameters from joint probability distribution of uncertain and sensitive parameters obtained from MCMC optimization with in vitro data
- Sampled parameters input into model. Model simulated under in vivo setting.
- Good agreement between model predictions and in vivo measurements

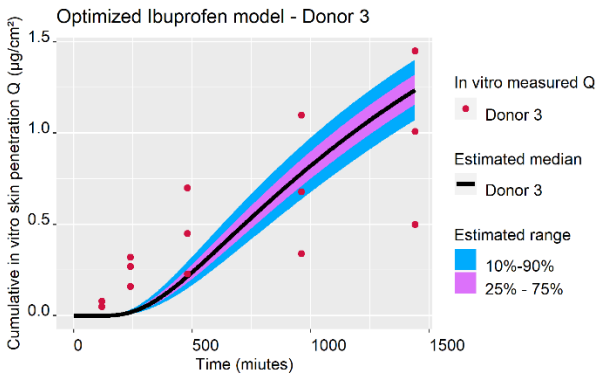
MODEL OPTIMIZATION RESULTS: IBUPROFEN

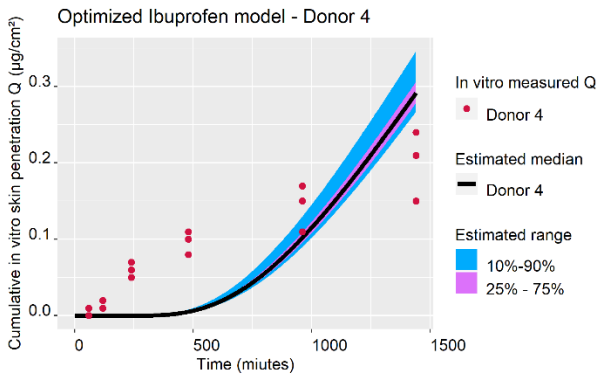
In vitro experiment (Hewitt et al., 2019):

- Dose applied: 2.51 µg/cm^2
- 24 hour, non-occluded experiment
- Solvent: phosphate-buffered saline (PBS)







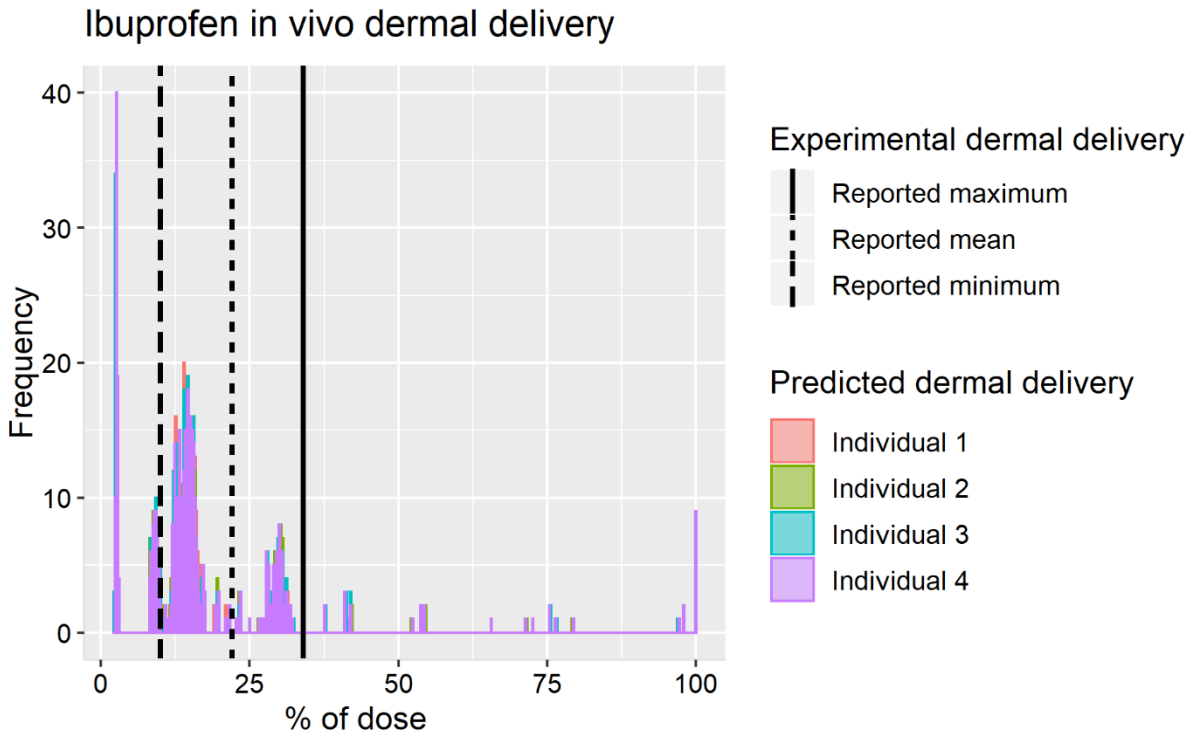


- Algorithm fitted model to cumulative mass of permeant in receptor fluid (Q)
- Fits to Donors 2 and 4 improved with later inclusion of follicle compartment (not shown)

PREDICTION OF IN VIVO ABSORPTION: IBUPROFEN

In vivo experiment (Kleinbloesem, Ouwerkerk, Spitznagel, Wilkinson, Kaiser, 1995)

- Dose: 1250 µg/cm^2
- 24 hour, occluded experiment
- Solvent: IbuGel (non-volatile)



In vitro-in vivo inference

- Ibuprofen-specific parameters learned from **in vitro** experiments performed under **non-occluded conditions** using a **volatile solvent**.

- Predictions tested against data obtained from **in vivo** experiments performed under **occluded conditions**, using **non-volatile solvent**.

- Able to predict in vivo despite different in vitro and in vivo contexts

HIGH PLASMA CONCENTRATIONS OF DERMALLY ABSORBED OF SUNSCREEN ACTIVE INGREDIENTS

JAMA | Preliminary Communication

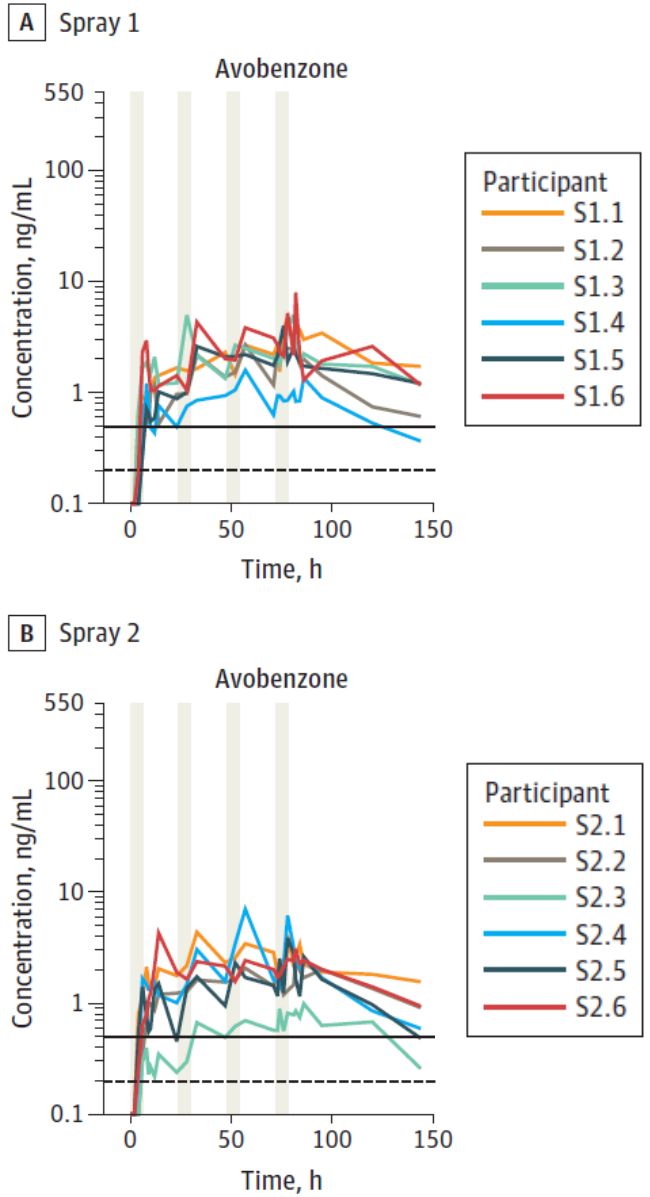
Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients

A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

INTERVENTIONS Participants were randomized to 1 of 4 sunscreens: spray 1 (n = 6 participants), spray 2 (n = 6), a lotion (n = 6), and a cream (n = 6). Two milligrams of sunscreen per 1 cm^2 was applied to 75% of body surface area 4 times per day for 4 days, and 30 blood samples were collected over 7 days from each participant.

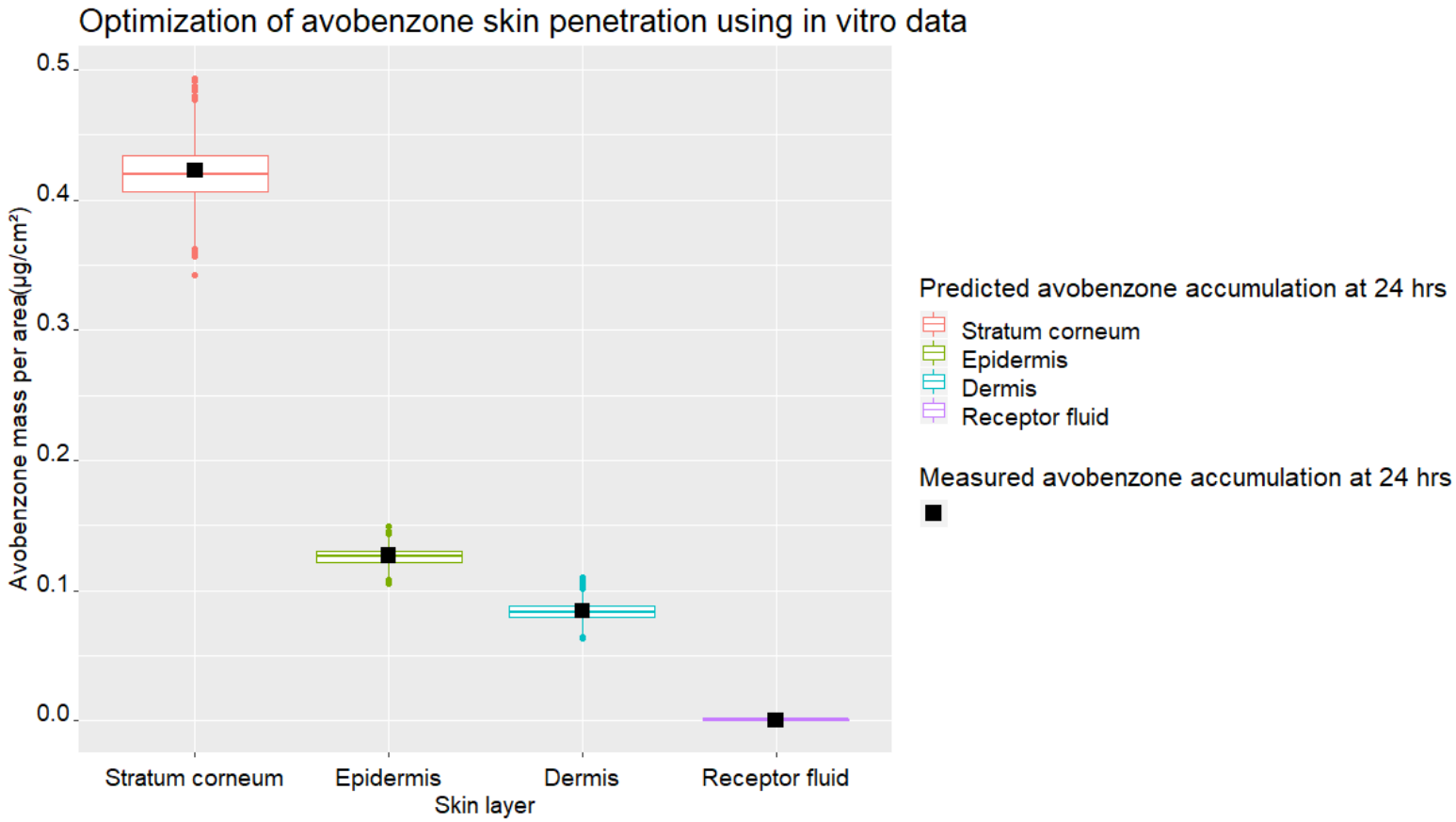
MAIN OUTCOMES AND MEASURES The primary outcome was the maximum plasma concentration of avobenzone. Secondary outcomes were the maximum plasma concentrations of oxybenzone, octocrylene, and ecamsule.



MODEL OPTIMIZATION RESULTS USING IN VITRO SKIN PENETRATION EXPERIMENT DATA FOR AVOBENZONE

Used methodology to calibrate model using avobenzone in vitro skin penetration data kindly provided by **A. Najjar & D. Lange, Beiersdorf.**

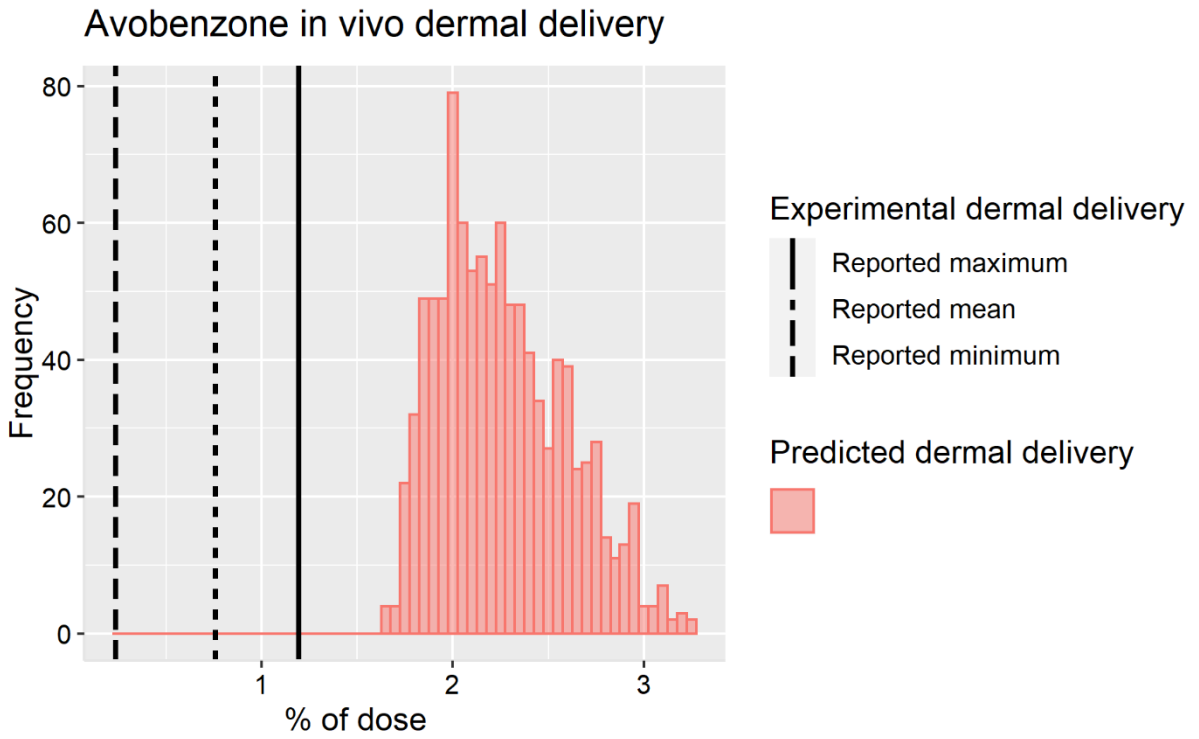
IVPT experiment measured accumulation of avobenzone in skin layers and receptor fluid at 24 hours following application of 8.45µg/cm^2 of avobenzone in an ethanol solvent to un-occluded skin.



Algorithm returns estimated joint distributions of avobenzone lipophilicity (5.9 ± 0.2), water solubility, fraction unbound in dermis, diffusion coefficient of unbound avobenzone in epidermis/dermis

ASSESSMENT OF MODEL'S PREDICTIONS OF AVOBENZONE DERMAL ABSORPTION IN VIVO

- Used QSPR prediction of avobenzone plasma clearance to estimate in vivo dermal delivery for Sprays 1 and 2 in Matta et al. from plasma concentrations



- Simulated model under in vivo setting using parameters obtained from optimization with IVPT data
- Close agreement between model predictions and in vivo experiments (despite uncertainty in clearance)
- Did not model metabolism of avobenzone in dermis, which would bring even closer agreement between predicted and experimental dermal delivery
- Have learned avobenzone-specific parameters relevant to dermal absorption that can be used in modeling other formulations

SUMMARY

- A flexible, open source dermal absorption model based on the Kasting model is now available on github as part of the Open Systems Pharmacology platform: *https://github.com/Open-Systems-Pharmacology/Skin-permeation-model*

- Assessed the Kasting dermal absorption model
  - Model predictions compared against in vitro skin penetration data for 56 compounds reported in Hewitt et al., 2019. Model mostly overpredicts (Q_{abs})
  - For most compounds, model predictions within one order of magnitude of experimental observations

- Presented a workflow to learn compound-specific parameters relevant to dermal absorption from in vitro data and to use learned parameters in predicting in vivo skin penetration. Workflow tested on compounds used in cosmetics, pharmaceuticals and sunscreens

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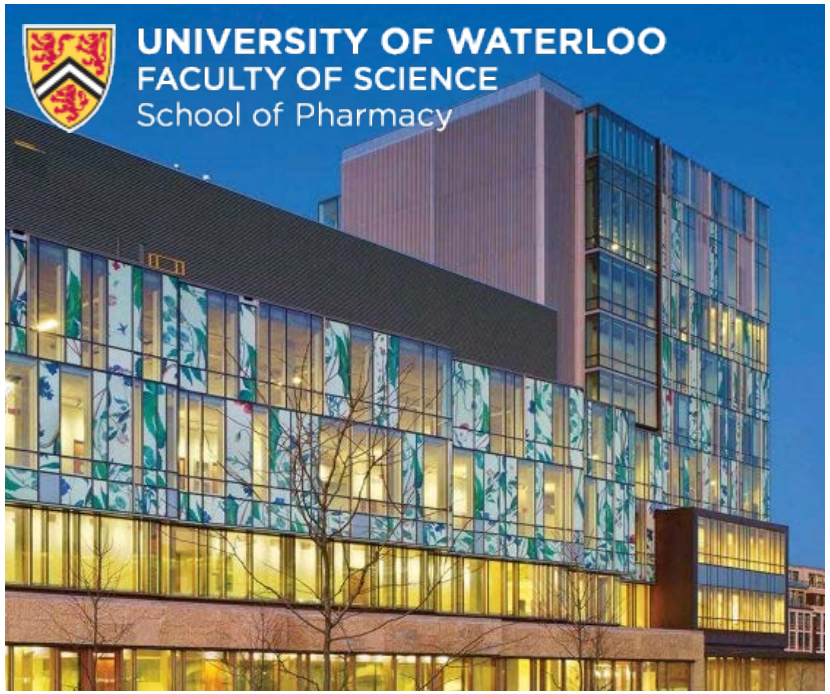

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