Mechanistic in silico inference of dermal absorption for chemical risk assessment

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Procter&Gamble

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

Overview

- Fundamental concepts in skin absorption
- Dermal Penetration in Risk Assessments
- Mechanistic in silico skin penetration model
- Workflow for inference of in vivo dermal absorption from in vitro data

Consumer Safety is Top Priority

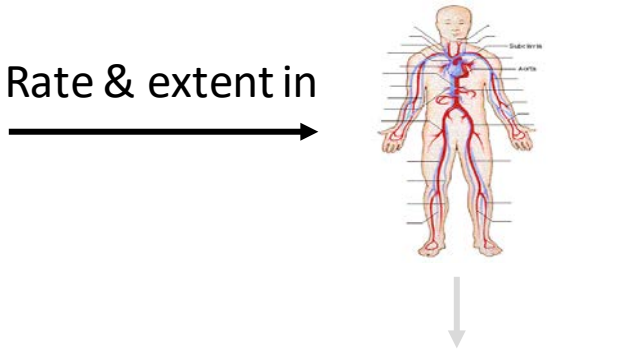
Skin and hair care cosmetics

Topical R_x and OTC

- Human Safety works to provide a positive assurance of objective safety for all products and consumer populations
- Objective safety standards are applied using state-of-the-art and scientifically sound methods
- Additional considerations may be required for safety assessments being submitted to a specific regulatory authority

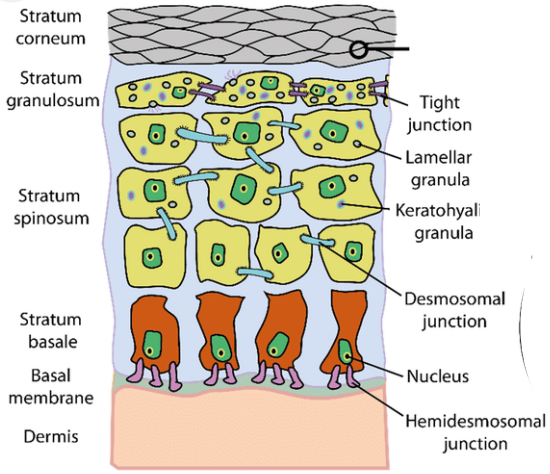
Skin Absorption

- Dermal Absorption – describes the transport of a substance from the skin surface into the systemic circulation
- For chemicals that contact the skin, dermal absorption a key consideration in chemical risk assessments:
  - How fast?
    - Rate - permeability coefficient, Kp (cm/h), flux (ug/cm^2/min)
  - How much?
    - Extent – cumulative mass or percent of applied dose absorbed (ug or %)
  - Where?
    - Disposition in skin sublayers, blood or tissues



- Guideline documents describing the experimental data generation and analysis (e.g., OECD No. 28, 156, 427, 428; WHO, 2006; SCCS NoG, 2018; ECETOC, 2013; EFSA, 2017; FDA-2018-D-1456)

Skin Structure and Function



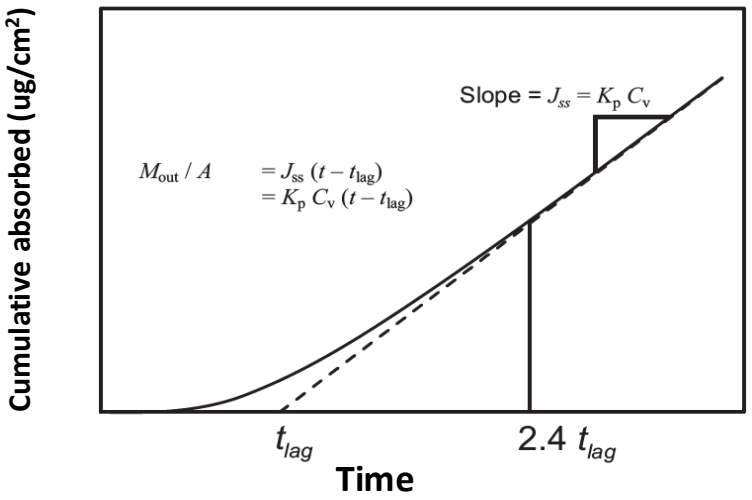
- Skin is a highly complex, multi-layered organ:
  - Epidermis
    - 50-200 μm thick
    - Stratum basale, S. spinosum, S. granulosum, S. corneum
    - Keratinocytes (viable nucleated cells; 95% of epidermal cells)
    - Corneocytes (flattened, dead, terminally differentiated anucleated keratinocytes)
    - 28 day turnover period
  - Dermis
    - Variable thickness depending on region
    - Primarily fibrous connective tissue (collagen)
  - Appendages (hair follicles, eccrine and apocrine sweat glands)
- Skin provides a barrier function between the internal and external environment:
  - Inward/outward movement of water and substances
  - Thermal regulation
  - Protection against damage from toxic substances, microbes, mechanical insults, UV radiation

Volz, et al., International Journal of Molecular Sciences 16(4):6960-77 · April 2015

Influencing Factors of Skin Absorption (partial list)

Phys-Chem Properties

- Molecular Weight
- Lipophilicity
- Ionization
- Solubility in formulation/vehicle
- Solubility in skin compartments
- Volatility



Skin Type & Condition

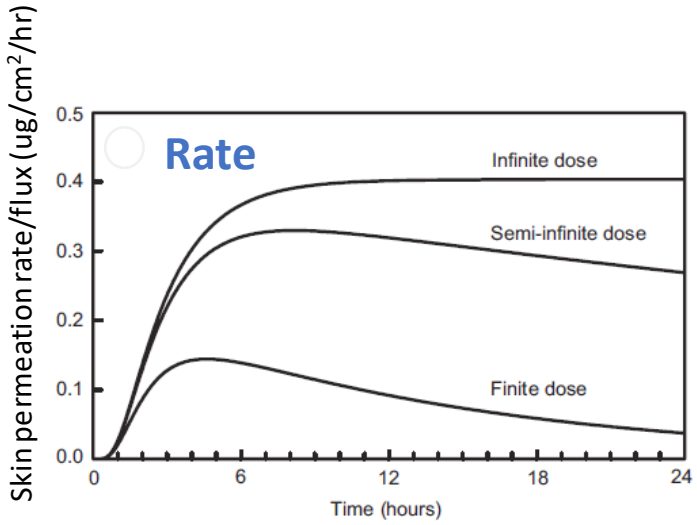
- Species of skin
- Age (healthy adult, preterm neonate, geriatric population)
- Physical conditions of the skin
  - Skin temperature (changes in blood flow in vivo)
  - pH (formulation/skin layers)
  - Occluded/non-occluded
  - Hydration state
  - Hair density
  - Compromised skin
- Part of the body exposed / skin thickness
  - Scrotum<forehead< scalp<back=abdomen<palms= soles of feet

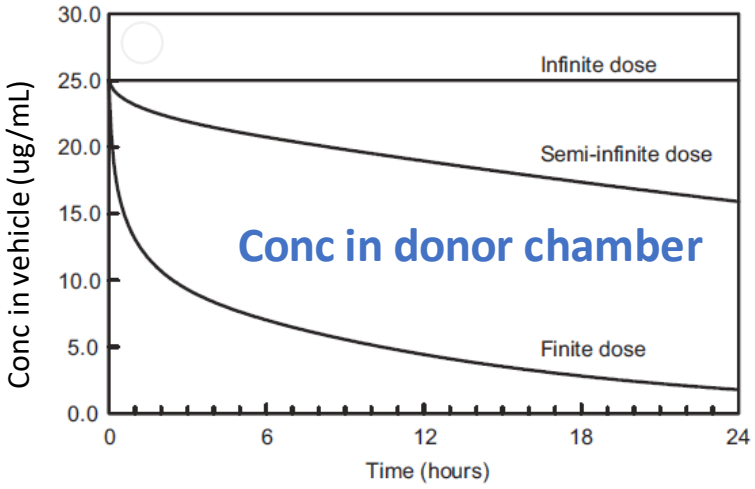
Exposure Scenario

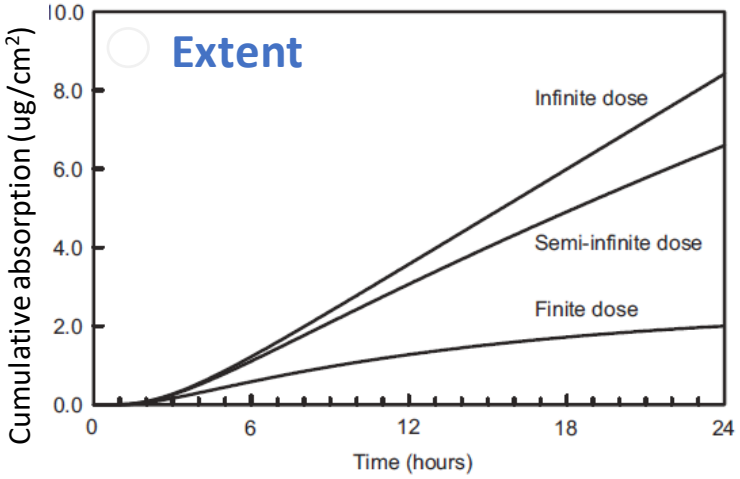
- Applied amount of formulation/vehicle
- Concentration of test substance
- Duration of exposure (rinse-off vs leave-on)
- Frequency of exposure
- Formulation type – petrolatum vs lotion vs organic solvent
- Co-solvents and modulating effects

Infinite vs Finite Exposure

Depending on the exposure scenario (i.e., dose applied, vehicle/formulation composition, skin conditions), the rate of skin permeation and the amount absorbed can vary significantly







Water solubility = 25 ug/mL
SC/water partition coefficient = 200

WHO, 2006

Difficult to express the skin penetration of a substance using a single value or metric

- Skin penetration data from one study cannot be assumed to be applicable to a different formulation or application scenario, particularly when expressed as % of applied dose.
- In ideal situations, experimental dermal absorption data would be generated under conditions closely mimicking the ‘in-use’ exposure condition that is being evaluated for toxicological risk.
- Although the assumption of 100% dermal absorption can be used as a ‘worst-case’ estimate of dermal absorption, this is an unreasonable conclusion given the protective barrier properties of the skin, primarily stratum corneum layer, and based on several experimental datasets showing that the dermal absorption of chemicals is less than 100%.

Mechanistic Skin Pen Model Objectives

- Implement a mechanistic dermal absorption model into freely available open-source modeling platform.
- Assess and improve the predictive performance of the model's estimates of skin penetration for in vitro finite and infinite dose experiments.
- Apply the model to address data gaps for untested chemicals and scenarios.
- Develop a workflow that integrates the dermal absorption model with existing in vitro skin penetration data to estimate in vivo dermal absorption.

Open Systems Pharmacology Suite

PK-Sim

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

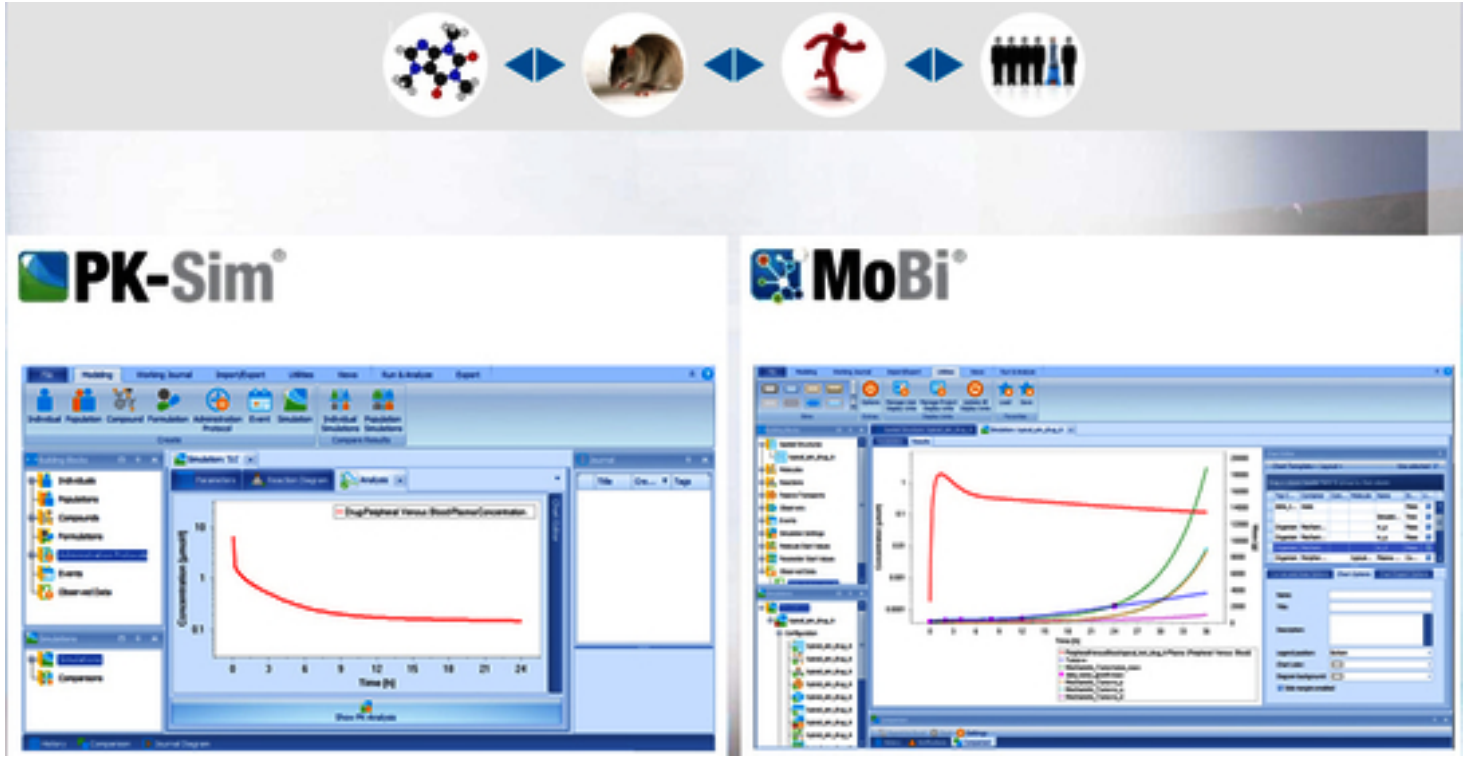
MoBi

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

OSPSuite-R

- R interface to PK-Sim and MoBi models.

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



OPEN SYSTEMS PHARMACOLOGY

The mechanistic UB/UC model of skin penetration, implemented in MoBi (Open System Pharmacology Suite)

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 ☆

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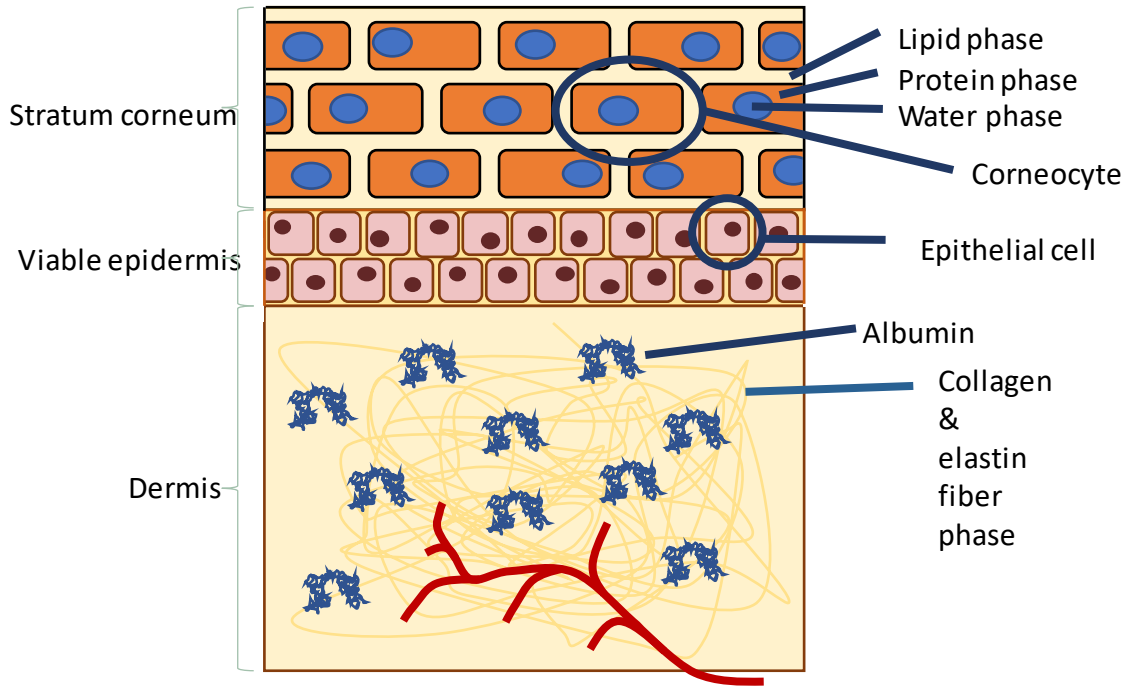
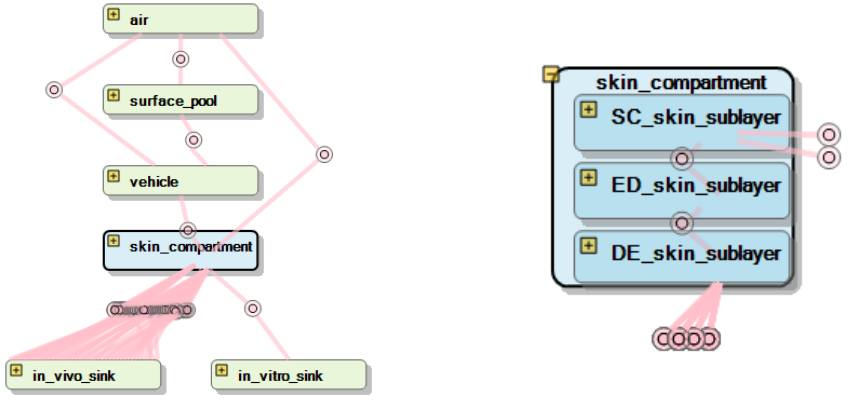


- **One dimensional partial differential equation representation of skin permeation**
- **Inputs include descriptors of:**
  - The applied permeant (physical/chemical properties)
  - Applied formulation
  - Skin condition
  - Experimental conditions
  - Application protocol
- **Outputs:**
  - Total accumulation in each skin layer and on skin surface
  - Flux and cumulative permeant amount that clears skin

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



Hewitt et al., 2019: recent in vitro skin penetration experiments to assess and train model

- **56 radiolabeled compounds tested in vitro using finite doses (10 uL/cm^2) in saline, ethanol or acetone vehicles.**
- **IVPTs were performed in triplicate for each of four individual donor skins under non-occluded conditions.**
- **Paper reports kinetic receptor fluid data and recovered amounts in skin surface, SC, epidermis & dermis at end of the 24 hr experiment.**
- **Paper lists in vivo measures from the literature for 7 compounds.**

RESEARCH ARTICLE

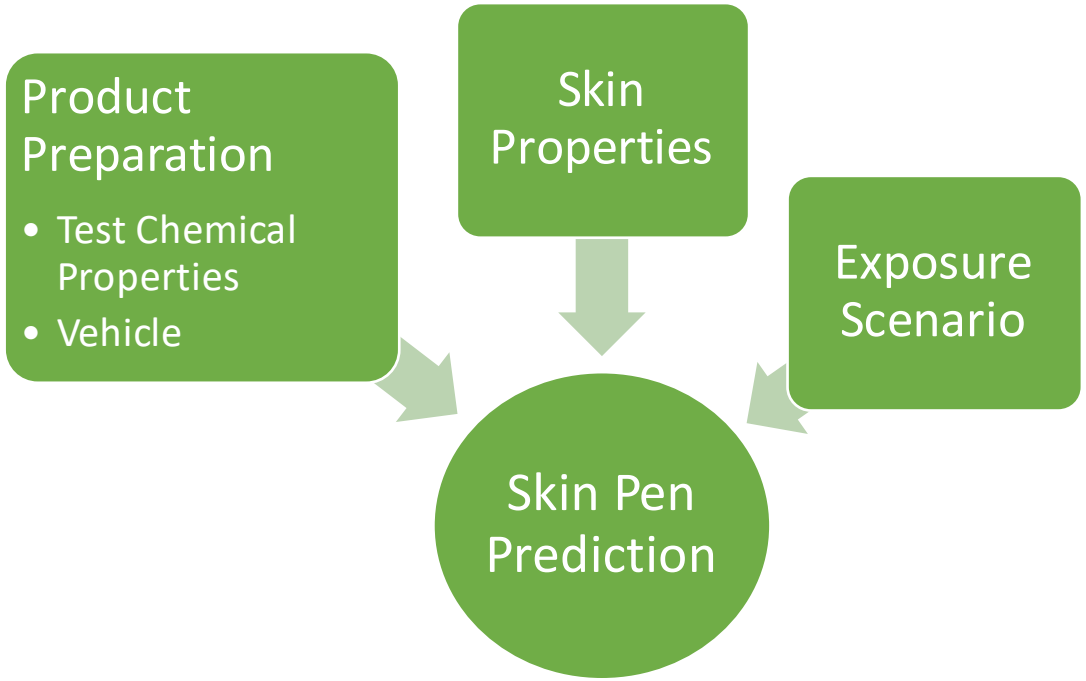
Journal of Applied Toxicology WILEY

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

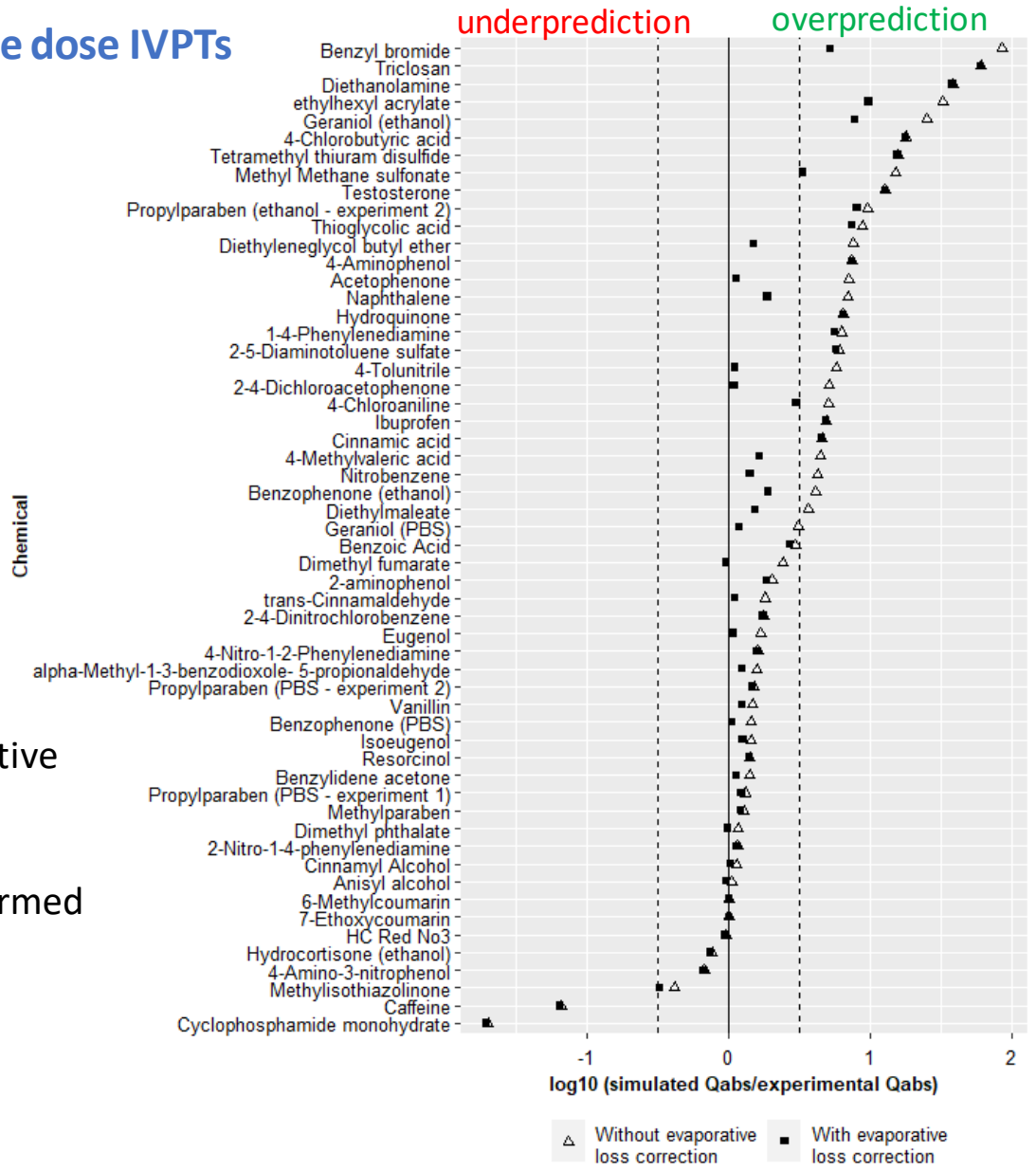
Nicola J. Hewitt[1] | Sébastien Grégoire[2] | Richard Cubberley[3] | Hélène Duplan[4] | Joan Eilstein[2] | Corie Ellison[5] | Cathy Lester[5] | Eric Fabian[6] | Julien Fernandez[7] | Camille Géniès[4] | Carine Jacques-Jamin[4] | Martina Klaric[1] | Helga Rothe[8] | Ian Sorrell[3] | Daniela Lange[9] |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

DOI: 10.1002/jat.3913

Performance assessment of MoBi model predictions of skin penetration



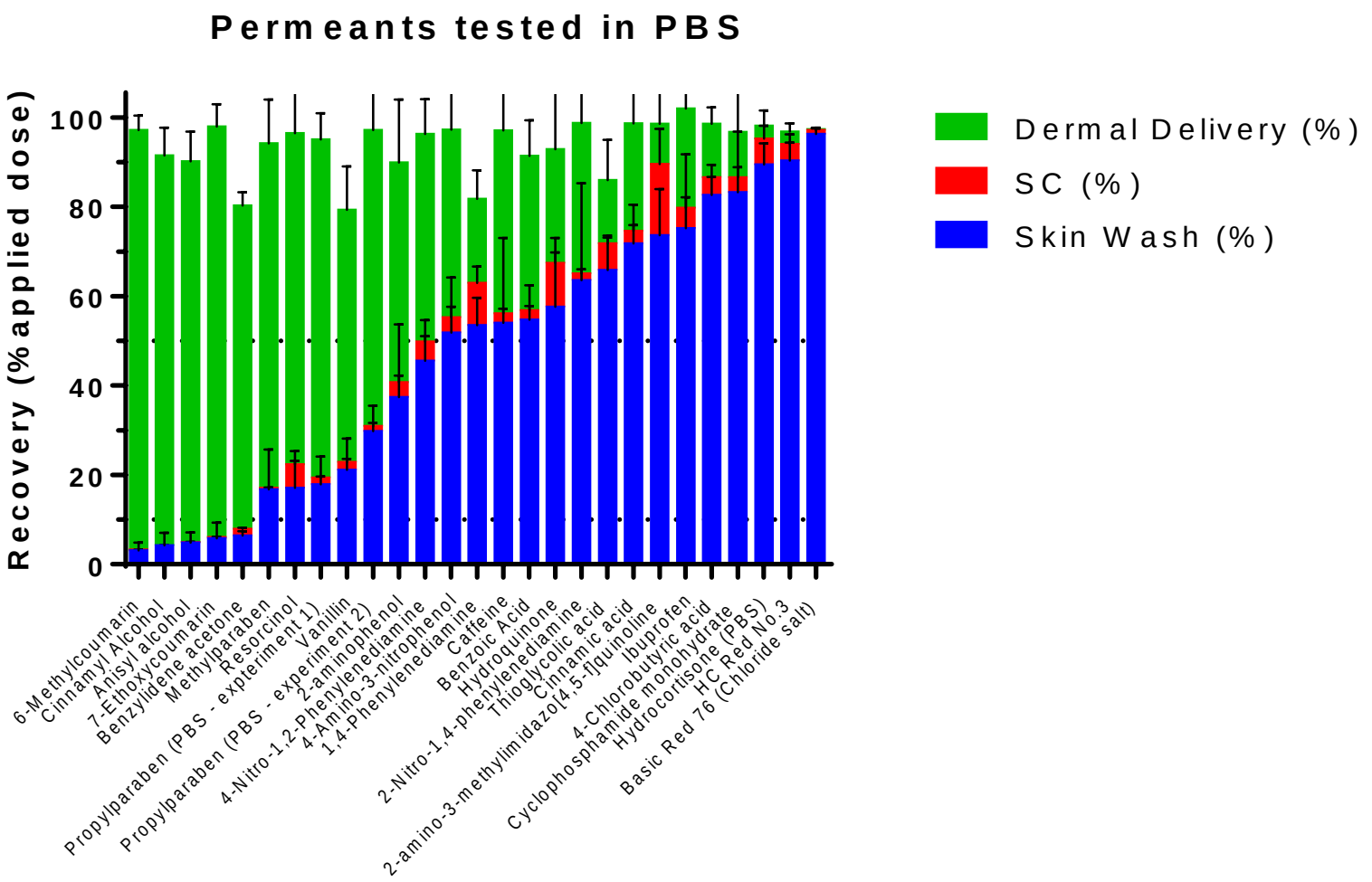
Finite dose IVPTs



- For each compound, simulations were performed to estimate cumulative permeation into receptor fluid at 24 hrs (Qabs)
- Several compounds were found to be volatile; simulations were performed with and without correction for chemical volatility
- Model predictions were mostly within a single order of magnitude of measured values, and tended to overpredict Qabs

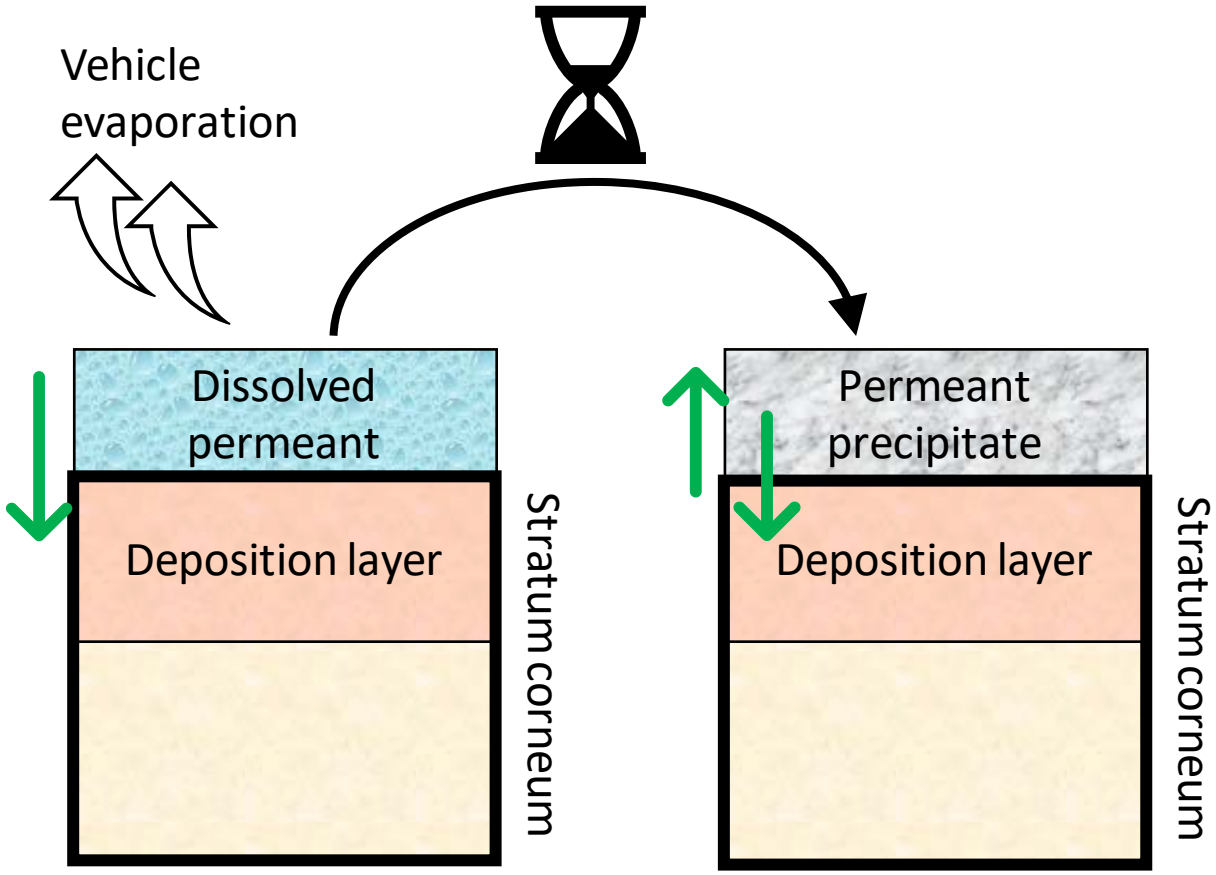
A substantial amount of the dose for many compounds tested in saline did not permeate the skin. Most of the test material was found unabsorbed in the skin surface wash.

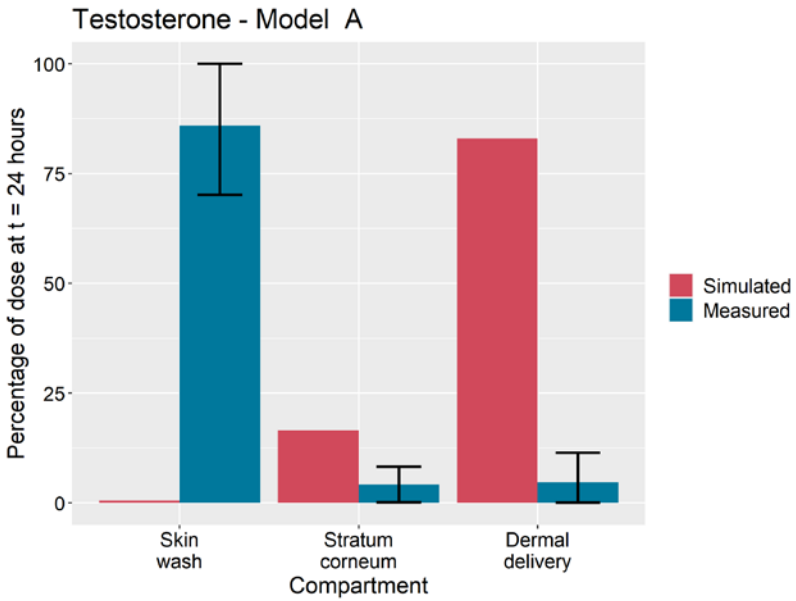
- These findings provide motivation to further review the experimental data and underlying assumptions of the vehicle and chemical disposition descriptions within the model

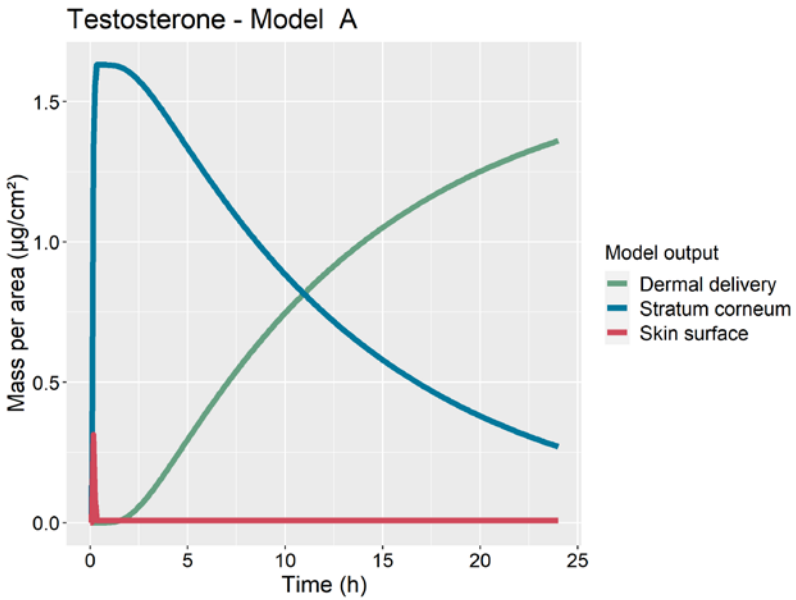


Model overpredicts skin permeation for most experiments in Hewitt et al. 2019

Model A - Continuous flow model
(Dancik et al., 2013)



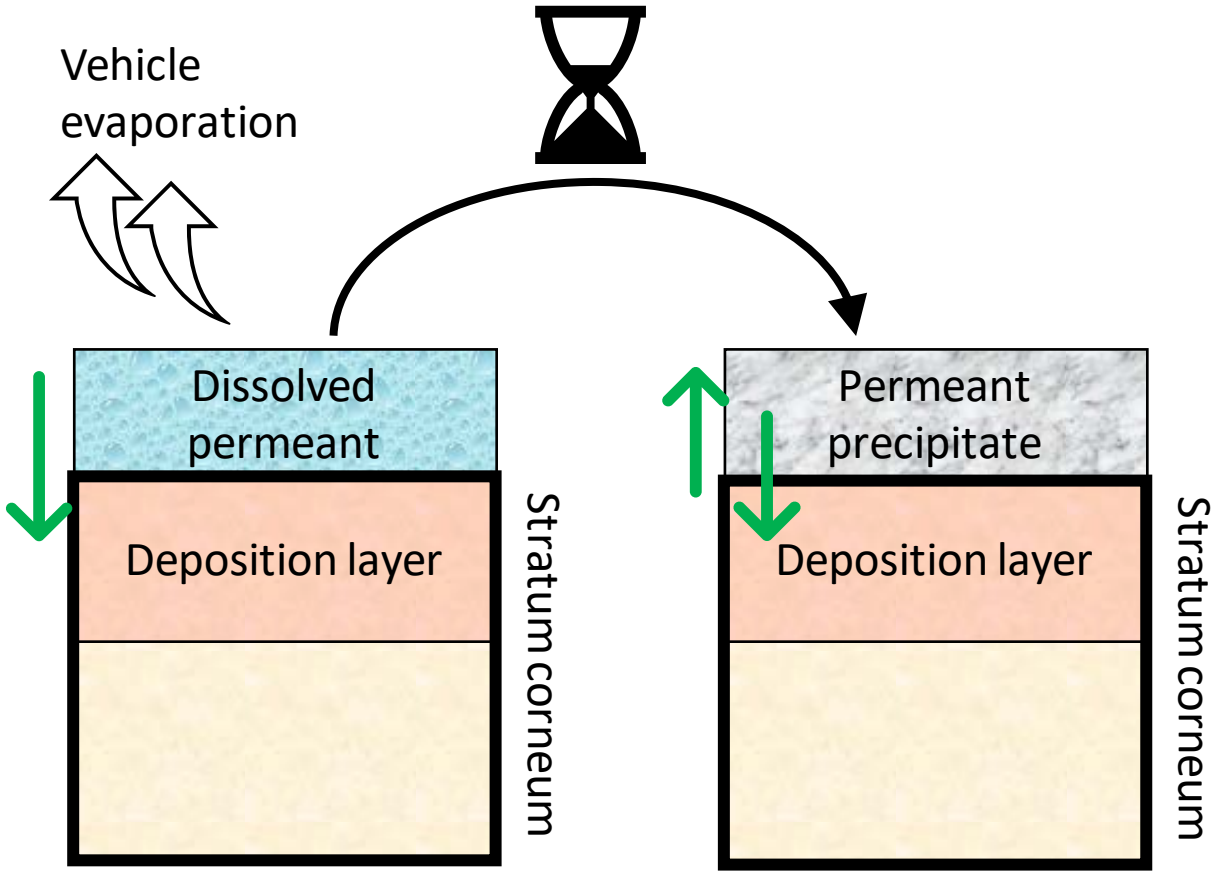




- Equilibrium permeant distribution at vehicle/SC interface
  → continuous flow of permeant from vehicle to SC
- Fixed deposition layer capacity

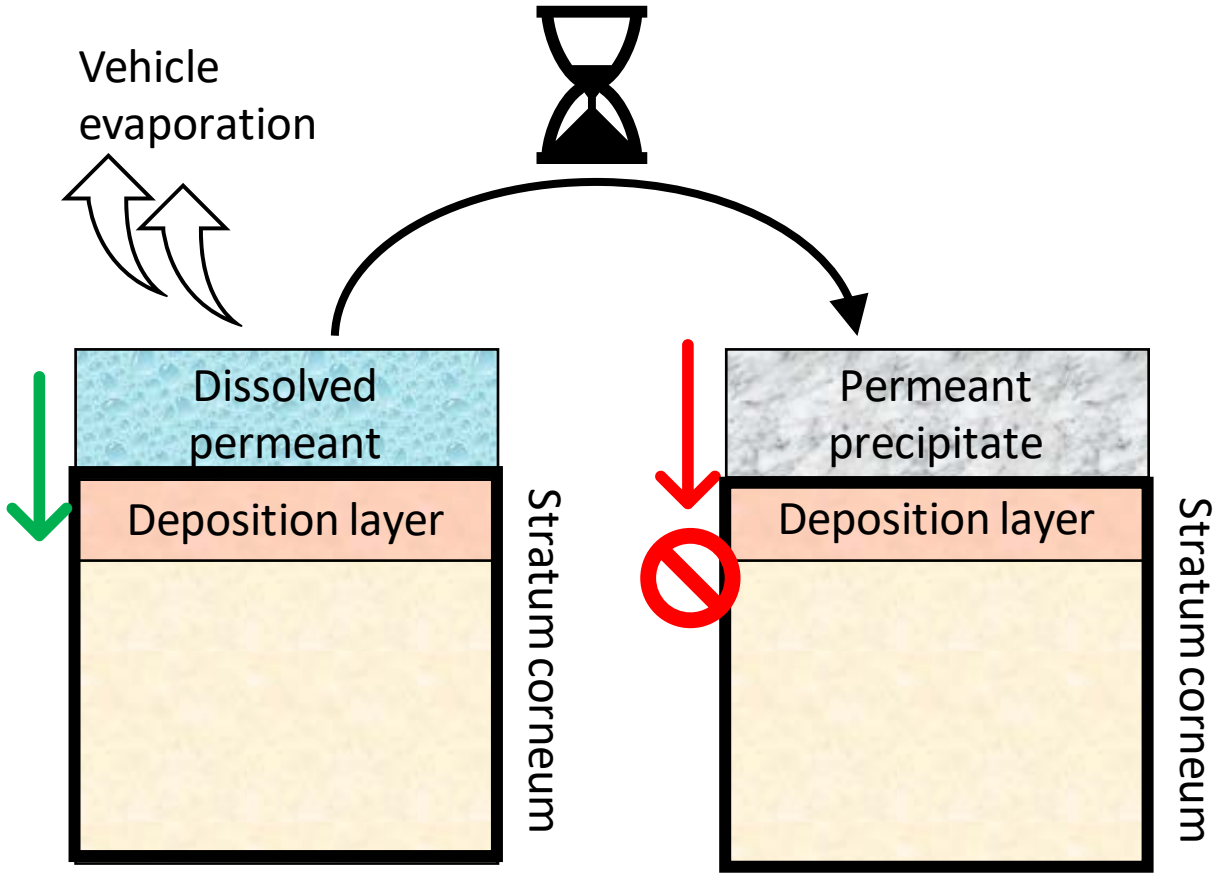
Modeling of permeant disposition at the volatile vehicle/SC interface

Model A - Continuous flow model
(Dancik et al., 2013)



- Equilibrium permeant distribution at vehicle/SC interface
  → continuous flow of permeant from vehicle to SC
- Fixed deposition layer capacity

Model B - Precipitation model
(Hamadeh et al., 2021)



- No vehicle to SC flow of permeant following vehicle evaporation
- Vehicle-dependent deposition layer capacity

Optimization of Model B (precipitation model) using in vitro data

Hewitt et al. 2019 dataset includes three compounds tested in both saline and ethanol vehicles:

- Benzophenone (MW = 182, log P = 3.18)
- Propylparaben (MW = 180, log P = 3.04)
- Hydrocortisone (MW = 363, log P = 1.61)

For each vehicle (saline and ethanol), we optimized:

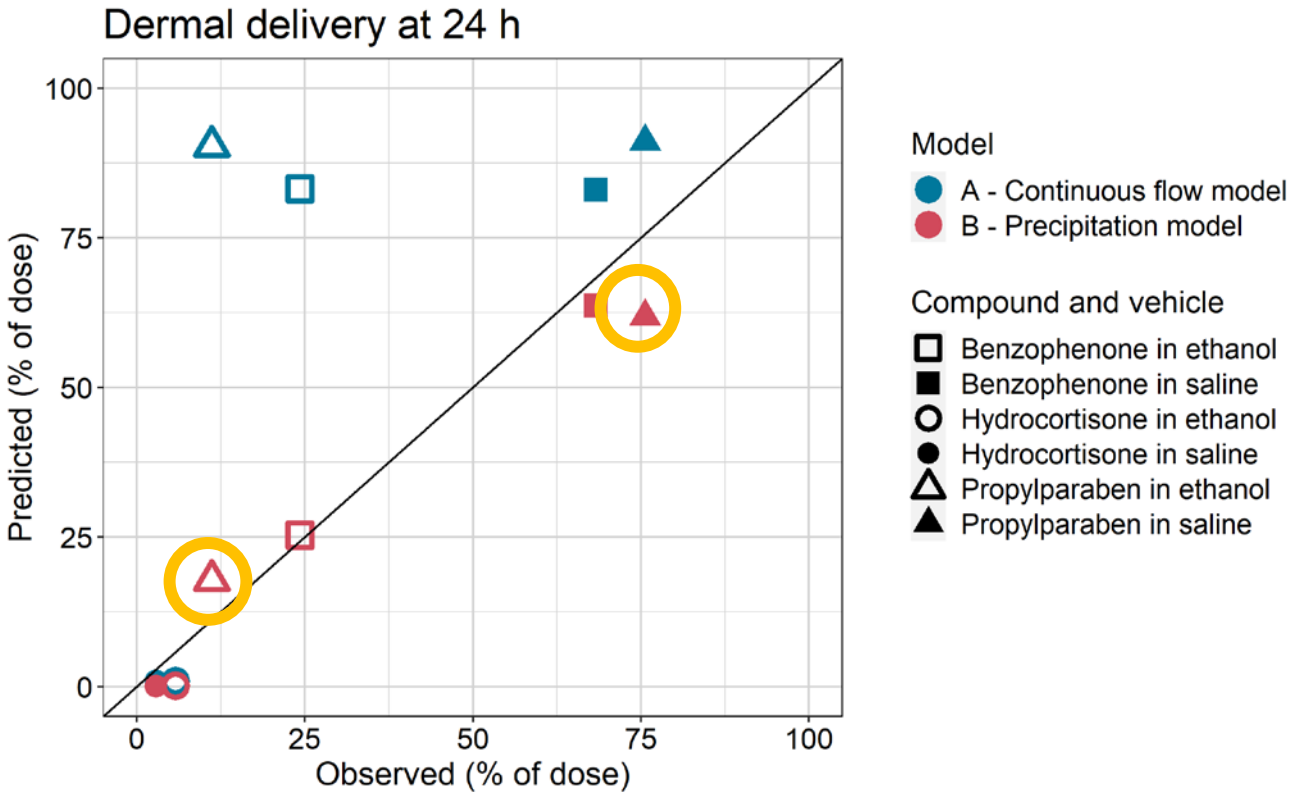
- Vehicle evaporation rate
- Deposition layer capacity

Qualitative results as expected:

- Ethanol vehicle evaporates faster than saline
- Ethanol is penetration enhancing ⟶ greater deposition layer saturation capacity

Note Propylparaben in saline vs in ethanol:

Ethanol vehicle evaporates faster than saline vehicle
⟶ Faster precipitation of propylparaben from ethanol vehicle
⟶ Lower dermal delivery under ethanol vehicle

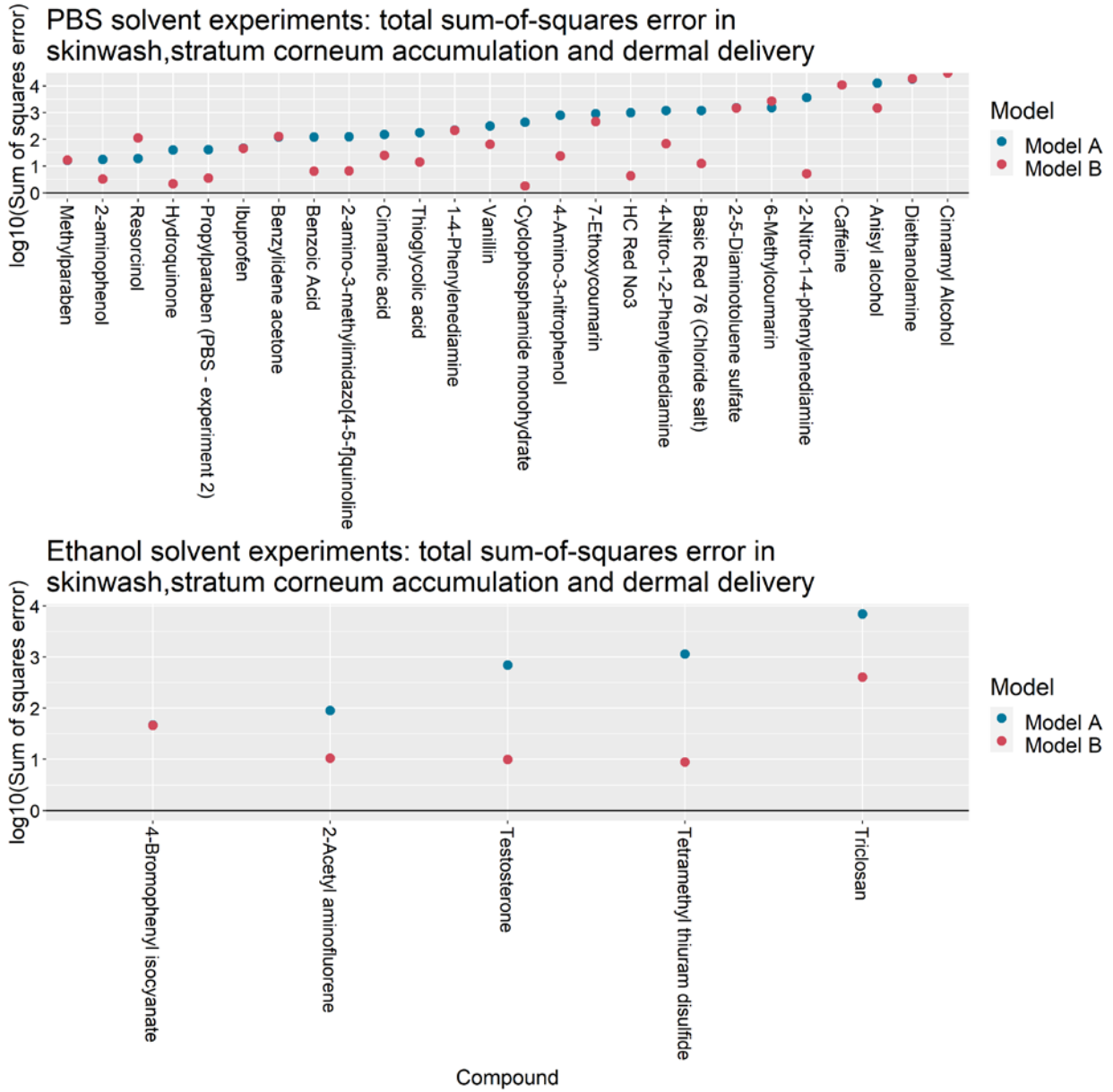


Hamadeh et al., *Pharmaceutics*, 2021

Model B (precipitation model) + learned vehicle-specific parameters yield improved model estimates across compounds

Model B – precipitation model

- Lower total sum of square error among 29/31 compounds.



Hamadeh et al., *Pharmaceutics*, 2021

Incorporating experimental data to improve model estimates

- Took advantage of the mechanistic nature of the model for learning *vehicle-specific parameters* using in vitro data for three compounds.

- Improved model predictions of absorption of *other compounds* under the in vitro context based on the
  - *learned ethanol vehicle-specific model parameters*
  - *learned saline vehicle-specific model parameters*

- *Next:* a workflow for learning *compound-specific* parameters from in vitro data for to improve predictions of of the model to predict in vivo dermal absorption

Mechanistic models – mechanistic decomposition of model uncertainty!

USER INPUTS
Phys/chem properties
Vehicle properties
Skin properties
Ambient conditions

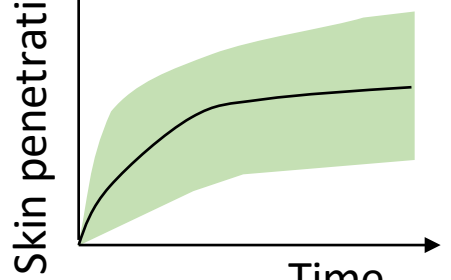
MoBi DERMAL MODEL

MODEL PARAMETERS
- Vehicle/SC partitioning
- SC diffusivity
- SC/epidermis partitioning
- Epidermis diffusivity
- Epidermis/dermis partitioning
- Dermis diffusivity
- Systemic update

DRUG TRANSPORT EQUATIONS

$$\frac{\partial c}{\partial t} = f\left(\frac{\partial^2 c}{\partial x^2}\right)$$

MODEL ESTIMATES



Stratum corneum diffusivity

Partitioning into lipid/corneocyte phases

Corneocyte phase diffusivity

Lipid phase diffusivity

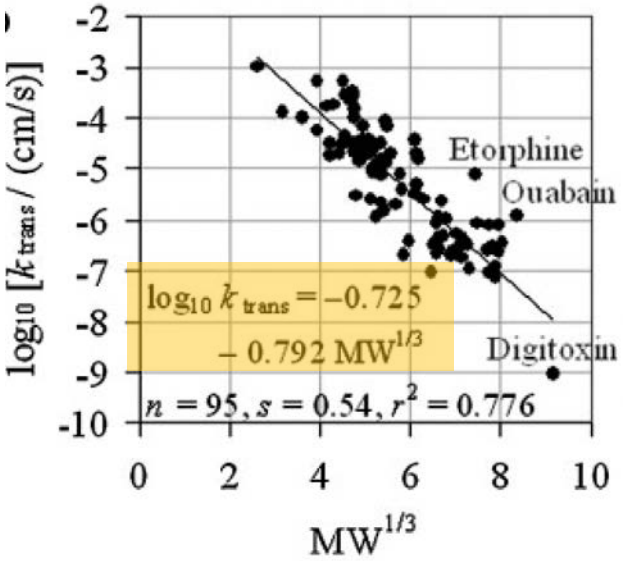
Trans-lipid bilayer permeability (k_{trans})

Lipophilicity

Molecular weight of permeant

Phys/chem user inputs

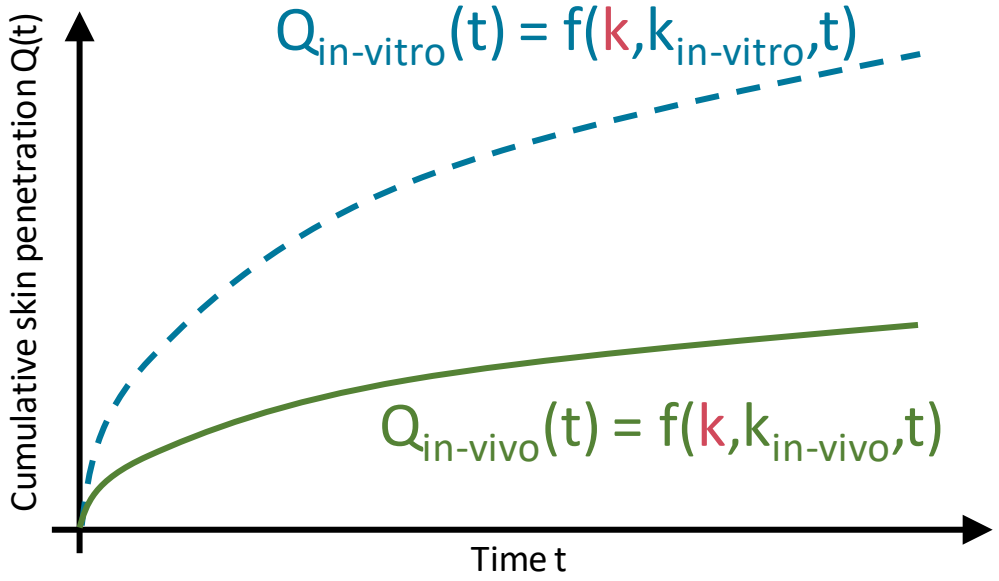
QSPR for k_{trans}



Learning model parameters from in vitro data to predict in vivo absorption

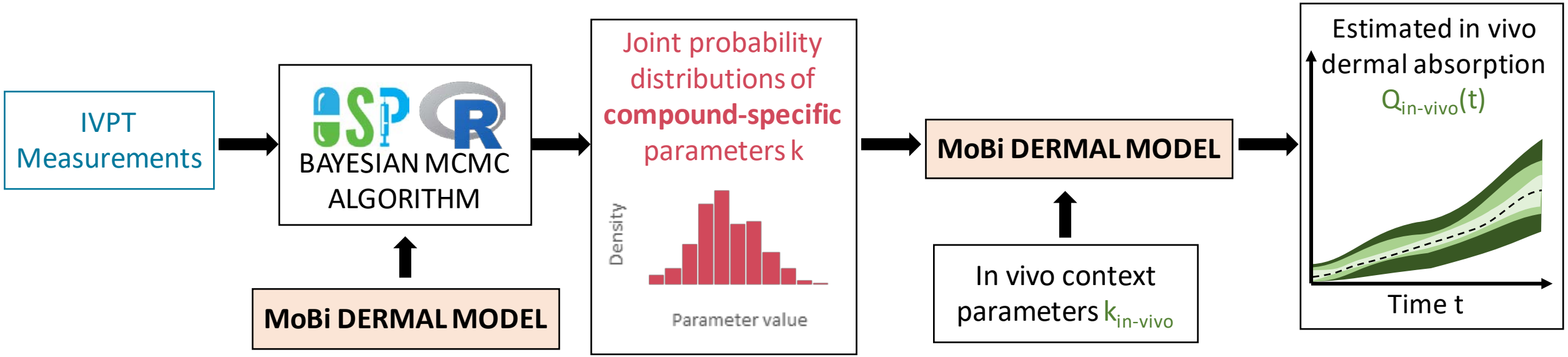
Skin penetration profiles are functions of

- Compound-specific parameters, k
- $k_{in\text{-}vitro}$, descriptors of in vitro skin conditions, experimental conditions, …
- $k_{in\text{-}vivo}$, descriptors of in vivo skin conditions, experimental conditions, …



Workflow

- Learn compound-specific parameter **joint probability distributions** from in vitro data
- Simulate in vivo context with learned compound-specific parameter **distributions** and in vivo context descriptors.



Application of the Bayesian in vitro-in vivo extrapolation workflow

- **In vitro dataset:** testosterone in vitro dermal absorption measured in (Hewitt, et al., 2019).

Hamadeh et al.,
J Pharm Sci, 111:3,2022

- **Extrapolation** to simulate in vivo experiments reported in (Feldmann & Maibach, 1969)

- **Parameters learned from in vitro data include:**
  - Trans-lipid bilayer permeability k_{trans} (a compound-specific parameter)
  - Stratum corneum thickness h_{sc} (an individual-specific parameter)

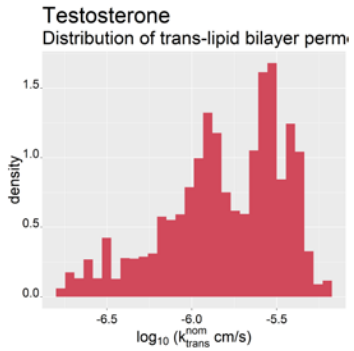
- **Multiple sources of variability between in vitro and in vivo contexts**

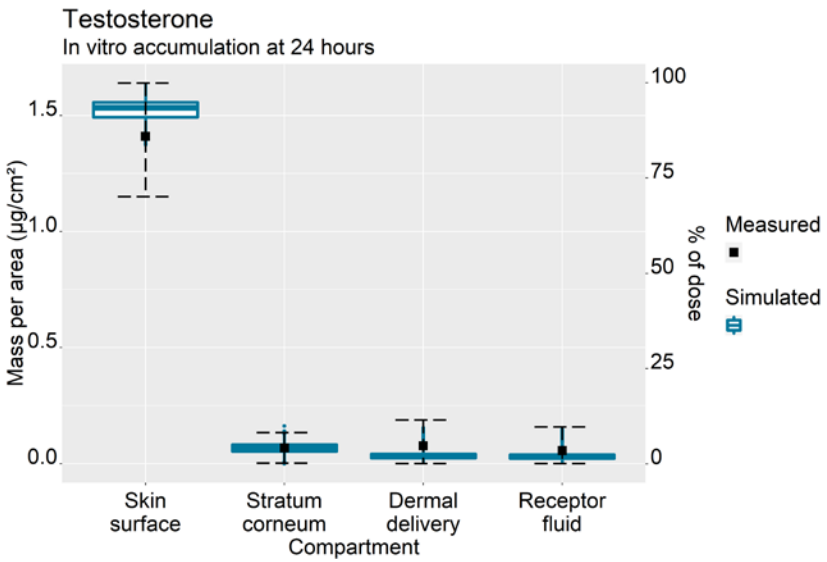
Descriptors of in vitro experiments
- **Vehicle:** Ethanol
- **Solubility in vehicle:** 106.2 mg/ml
- **Dose:** 1.64 µg/cm^2
- **Duration:** 24 hours
- **Stratum corneum thickness:** Uncertain (13-40 µm)

Descriptors of in vitro experiments
- **Vehicle:** Acetone
- **Solubility in vehicle:** Not reported
- **Dose:** 4 µg/cm^2
- **Duration:** 5 days
- **Stratum corneum thickness:** 13 µm

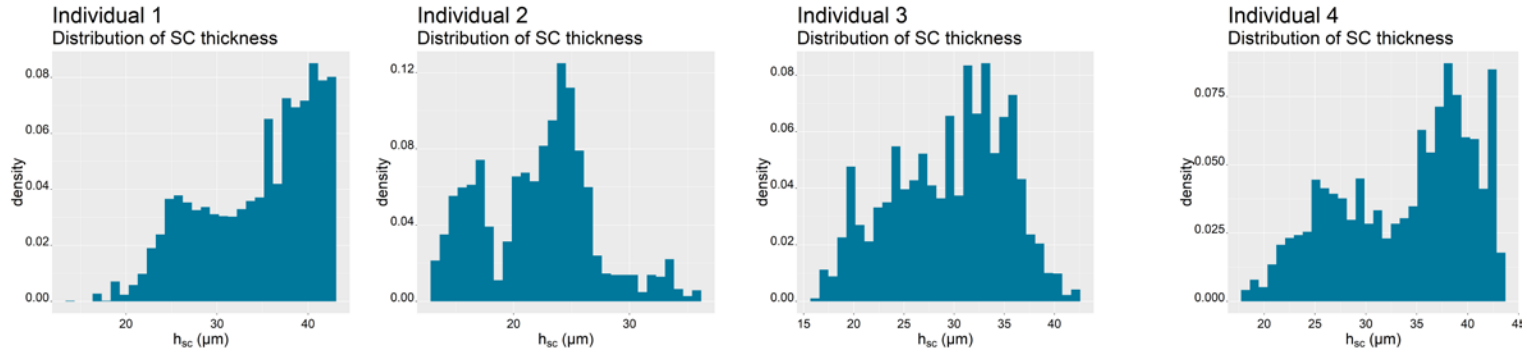
Visual predictive checks of model fits to in vitro data in Hewitt et al., 2019

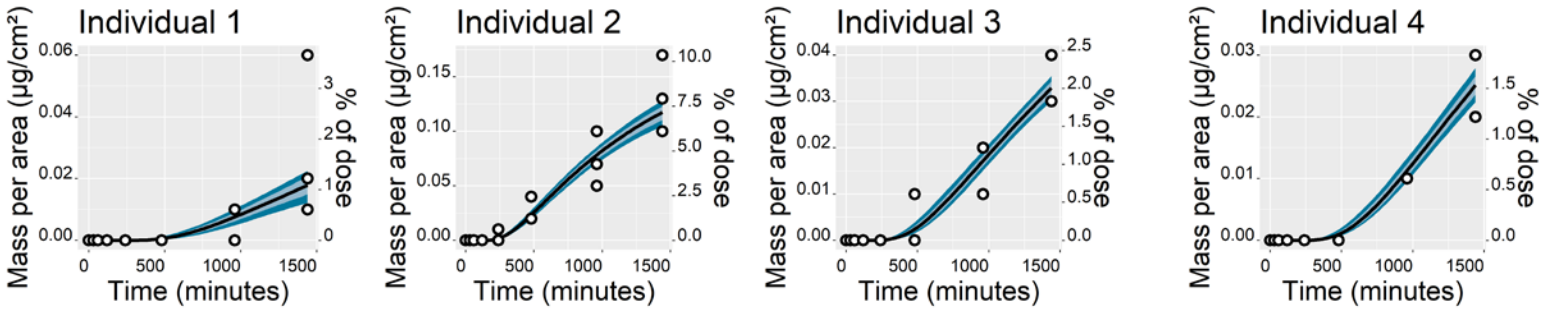
Learned compound-specific parameter distribution





Learned individual-specific parameter distribution





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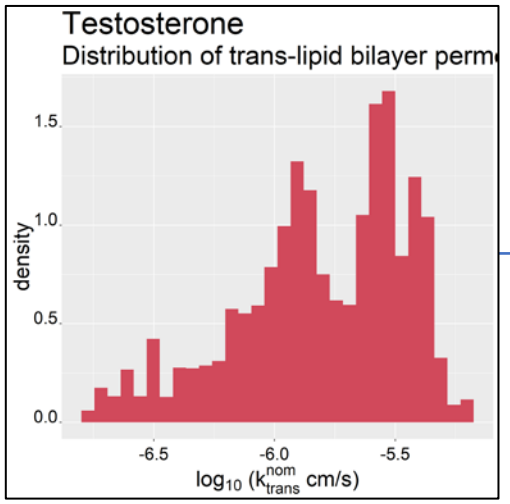
Extrapolating learned compound-specific parameters to model in vivo absorption

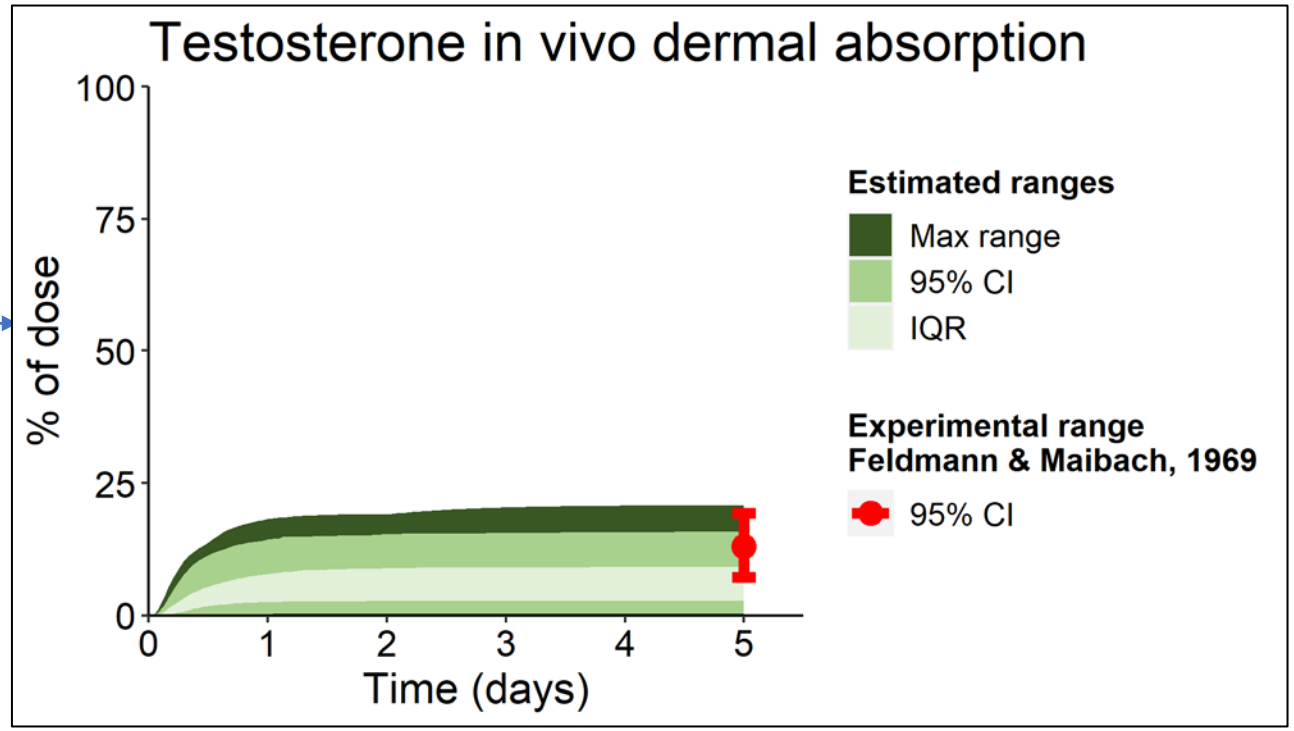
Learned compound-specific parameter distributions



MoBi DERMAL MODEL

Descriptors of in vivo context:

- Formulation properties
- Skin properties
- Ambient conditions



- Model updated with values of testosterone-specific parameters learned from Hewitt, et al., 2019 experiments.
- Model was set to simulate in vivo scenario of experiments in Feldmann & Maibach, 1969.
- Model estimates capture the range of dermal absorption seen experimentally.

Hamadeh et al., *J Pharm Sci*, 111:3,2022

- Due to model uncertainty, model also predicts scenarios where in vivo absorption is underestimated.
  - ➢ Effect of acetone on stratum corneum lipids? (Bond & Barry, 1988; Tsai, et al., 2001)

Conclusions

Mechanistic model

- Simulates dermal absorption of chemicals under a wide variety of skin conditions, ambient conditions, exposure conditions, application scenarios, formulations.
- Potential to reduce the time and cost burdens of conducting new experimental studies.

Learning mechanistic model parameters from data

- Mechanistic decomposition of model uncertainty.
- Identification of key quantities impacting dermal absorption.
- Enables *extrapolation* of learned parameters to predict skin penetration in novel scenarios.

Bayesian learning approach

- Learns joint probability distributions of model parameters within realistic uncertainty ranges/physiological limits.
- *At extrapolation:* model simulated with samples from learned joint distributions ⟶ extrapolated estimates account for any lack of parameter identifiability.

Limitations

Extrapolation must account for all differences between learning and intended scenarios: Skin hydration? Occlusion? Skin health? Humidity? Wind exposure? Application mode (leave-on, rinse-off)?

Mechanistic understanding of the intended scenario needed to mitigate uncertainty

- What is the impact of a complex vehicle on skin?
- How does a chemical partition between vehicle and skin?
- What is the impact on skin of an infinite dose?
- What is the impact of damaged skin?

Outreach

- Think about new experiments, datasets and mechanistic models to improve mechanistic understanding of skin penetration under new scenarios.
- Open Systems Pharmacology: a community of users to ask/discuss pharmacokinetic modeling questions.

Acknowledgements

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