THE FDA MODEL MASTER FILE

STANDARDIZATION OF M&S PRACTICES TO SUPPORT THE DEVELOPMENT AND APPROVAL OF DERMATOLOGICAL PRODUCTS

2024 OSP COMMUNITY CONFERENCE
2024 – 10 – 08

ABDULLAH HAMADEH, PHD

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

WHERE ELSE MIGHT A MODEL MASTER FILE BE USEFUL?

- Model Master File (MMF) framework and relation to dermal modeling
- FDA's efforts to standardize models
  - Workshops held in October 2022 and May 2023.
  - Publication: Fang et al., *The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA*. AAPS Journal, (2024) 26:28
- Models as a resource for:
  - Product development.
  - Shared science.
  - Regulatory review.
  - Streamlining drug approval processes.
- Models including:
  - PBPK, pop-PK, IVIVC model, drug-device models, immunogenicity models.

THE MECHANISTIC UB/UC MODEL OF SKIN PENETRATION, IMPLEMENTED IN MOBI (OSP 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 ☆

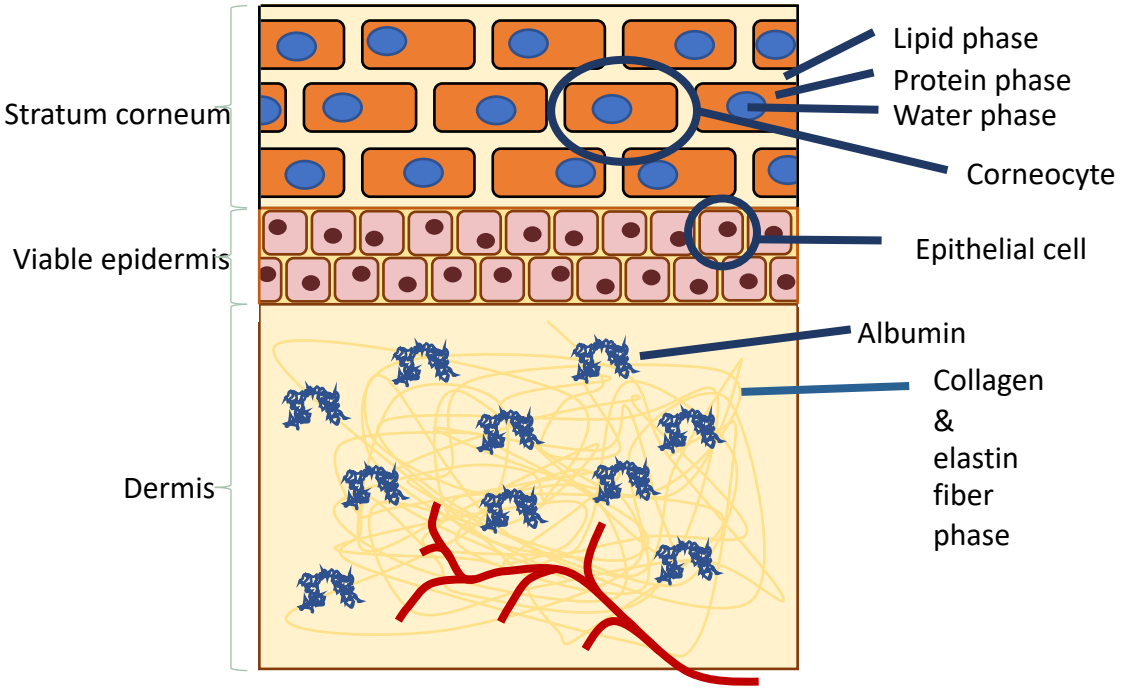
Yuri Dancik [a], Matthew A. Miller [b,*], Joanna Jaworska [a], Gerald B. Kasting [b]

[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

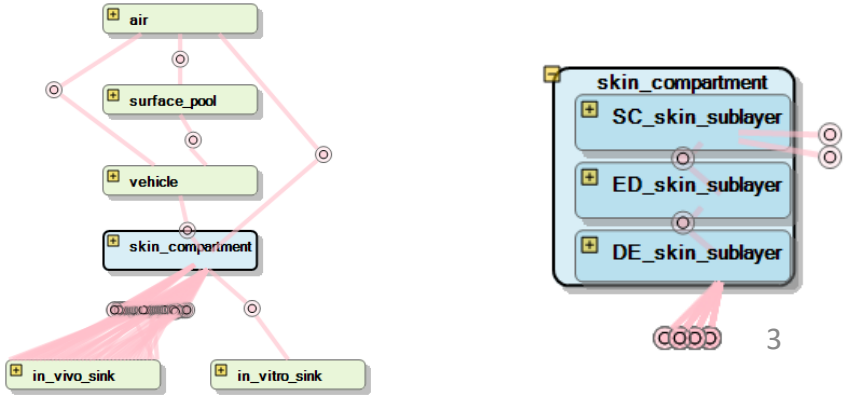
- **One dimensional partial differential equation representation of skin permeation**

- **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



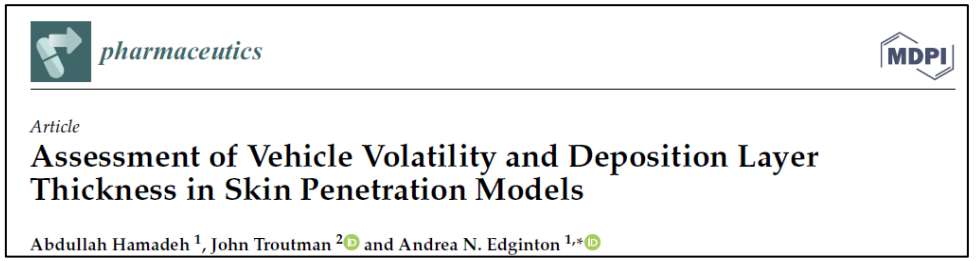
OSP DERMAL MODEL CONTRIBUTIONS TO MECHANISTIC MODELING OF DERMAL ABSORPTION

- **Model development**
  Empirical model of vehicle evaporation

- **Learning and extrapolation**
  How to train skin absorption models with in vitro measurement data to predict in vivo dermal disposition

- **Experiment design for model training and extrapolation**
  How to select/generate informative experimental data for robust model training and extrapolation

- **Data fusion from multiple diverse data sources**
  Learning sunscreen formulation effects from in vitro data, clearance from in vivo data, and extrapolating to new application scenario.



pharmaceutics

MDPI

Article

Assessment of Vehicle Volatility and Deposition Layer Thickness in Skin Penetration Models

Abdullah Hamadeh [1], John Troutman [2] and Andrea N. Edginton [1,*]

Journal of Pharmaceutical Sciences 111 (2022) 838–851

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

A Mechanistic Bayesian Inferential Workflow for Estimation of In Vivo Skin Permeation from In Vitro Measurements

Check for updates

Abdullah Hamadeh[a], John Troutman[b], Abdulkarim Najjar[c], Andrea Edginton[a,*]

[a] School of Pharmacy, University of Waterloo, Kitchener, ON N2G 1C5, Canada
[b] The Procter & Gamble Company, Mason, OH 45040, United States of America
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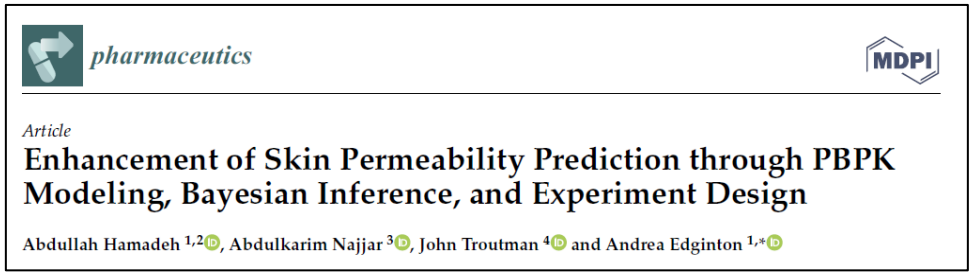


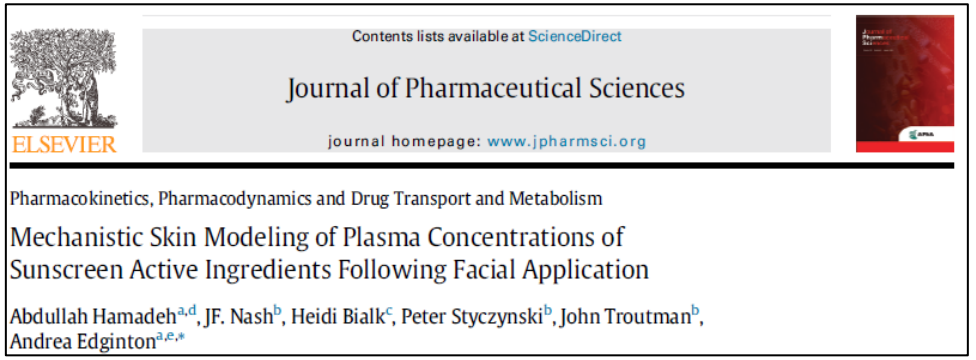
pharmaceutics

MDPI

Article

Enhancement of Skin Permeability Prediction through PBPK Modeling, Bayesian Inference, and Experiment Design

Abdullah Hamadeh [1,2], Abdulkarim Najjar [3], John Troutman [4] and Andrea Edginton [1,*]



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journal homepage: www.jpharmsci.org

ELSEVIER

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Mechanistic Skin Modeling of Plasma Concentrations of Sunscreen Active Ingredients Following Facial Application

Abdullah Hamadeh[a,d], JF. Nash[b], Heidi Bialk[c], Peter Styczynski[b], John Troutman[b], Andrea Edginton[a,e,*]

VIRTUAL BIOEQUIVALENCE SUCCESSFULLY USED IN GENERIC DRUG APPROVAL APPLICATION

- Paper discusses approval of an ANDA for:
  - **Test:** generic diclofenac sodium topical gel, 1%
  - **Reference**: Voltaren topical gel, 1%

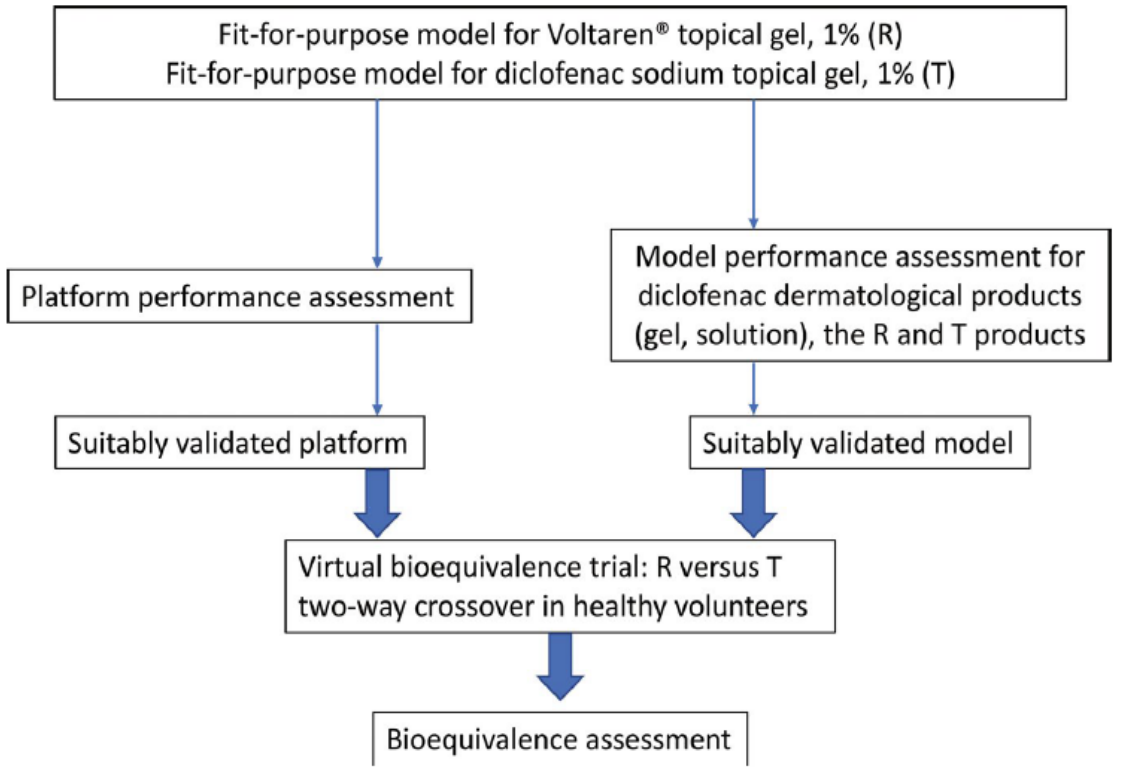
- First time a VBE assessment leverages dermal PBPK modeling and a **totality of evidence approach** resulting in ANDA approval.

- **Current product specific guidance for establishing BE diclofenac sodium topical gel, 1%:**
  - an in vivo BE study with PK end points in healthy volunteers
  - and an in vivo comparative clinical end point BE study in knee osteoarthritis patients

- **FDA waived the in vivo comparative clinical end point BE study** based on a validated model that predicts bioequivalence of test and reference at the presumed site of action (skin and synovial fluid).

Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

Eleftheria Tsakalozou | Andrew Babiskin | Liang Zhao



"Considering comparative clinical end point BE studies tend to be the least sensitive approach to detect formulation differences between a reference and test product, the Agency encourages generic drug applicants to use alternative BE approaches, such as modeling and simulation."

RATIONALE FOR MMF FRAMEWORK

Example demonstrated use of modeling to avoid a costly BE study

Consider several generics manufacturers each building their own models of the same reference drug, submitted separately.

Issues identified

Wasted Time: Regulatory agencies must review multiple models of the same reference drug repeatedly.

Inconsistent Science: Each virtual BE assessment is performed based on potentially different models of the reference drug.

Consequences

Models may represent different ADME mechanisms, leading to incongruity.

Regulators are aware of the discrepancies but cannot inform manufacturers.

Solution?

A unified accepted model could mitigate these issues, providing a common scientific basis for all applications.

Features of MMFs that add value:

- **Acceptance**: *model is validated*
  - (via, e.g. the OSP Qualification Framework).

- **Availability**: *model is available*
  - (from, e.g. GitHub).

- **Accessibility**: *the model is understood and modifiable.*
  - model is open source, model equations available through MoBi.
  - can modify absorption/dissolution for generics, retaining accepted systemic model

Title: Mechanistic in silico inference of dermal absorption for chemical risk assessment

Presenters: John Troutman and Abdullah Hamadeh

155 participants from 20 different countries

Do you use in silico skin penetration methods to inform (check all that apply)?

65%

a. Product innovation and development - 12%
b. Safety Assessment – 53%
c. Neither – 33%
d. Other – 2%

What are the barriers to using in silico models?

74%

a. Lack of regulatory acceptance - 50% **Acceptance**
b. Complexity to access and run simulations – 24% **Availability**
c. Skepticism with model structure, parameterization and applicability – 21%
d. Other – 5%

What would increase your confidence in applying/accepting model predictions?

84%

a. Demonstrate relevance and reliability using experimental data - 55% **Acceptance**
b. Availability of training materials (courses, tutorials, guidance documents) – 29% **Accessibility**
c. Access to model documentation – 16%

- **Limited sharing by developers**
  - Drug developers have little incentive to share models beyond regulatory submissions, making availability a challenge.

- **Closed source model limitations**
  - Closed-source models are restricted to licensed users, creating accessibility issues.
  - Limited ability to customize model for novel drug products.

- **Need for a standardized framework**
  - Agreement required across regulatory, academic, and industrial sectors on:
    - Model description, verification, and validation (acceptance).
    - Documentation format and parameterization.

- **Defining valid contexts of use**
  - Clear boundaries needed for model applicability:
    - Small vs. large molecules, formulation classes, and populations.

A pathway to MMF development could be through **academic-industrial partnerships**.

- **Incentive for industry:** regulator acceptance of relevant modeling platform opens pathway to modeling studies in lieu of clinical studies:
  - OSP dermal model (outcome of University of Waterloo partnership with P&G)
  - Models of release from special classes of formulations (long acting injectables)
  - Models of release from devices

- **Incentive for academia:** student training, networking, development of computational tools for further research

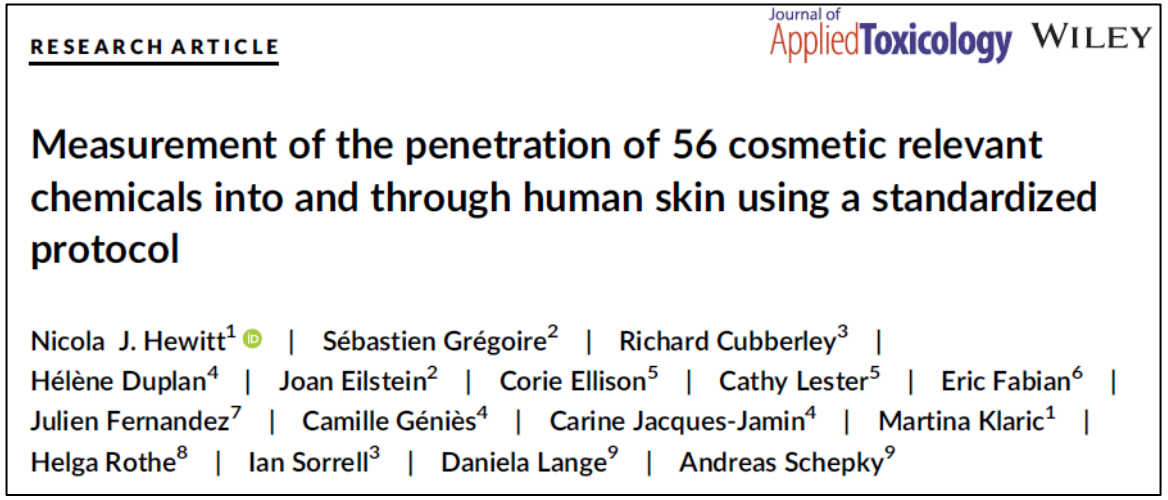
- **Our ongoing efforts with P&G:**
  - Development of OSP dermal model validation platform
  - Shiny app interface
  - OSPSuite R in the background.
  - Aim to show validation of OSP dermal model against literature datasets

Modeling dermal absorption

- High sensitivity to application context (formulation, dose).
- Inter-individual variability: stratum corneum thickness, hydration, sebum content
- Within-individual variability across anatomical sites
- Inter-occasion variability due to vehicle metamorphosis

Validation:

- Common in vitro testing protocols: IVRT, IVPT
- Large volume of published data, in vitro and in vivo
- Variety of measurement points: skin surface, stratum corneum, epidermis, dermis, percutaneous amounts.



RESEARCH ARTICLE

Journal of AppliedToxicology 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]

Toxicology in Vitro 69 (2020) 104990

Contents lists available at ScienceDirect

Toxicology in Vitro

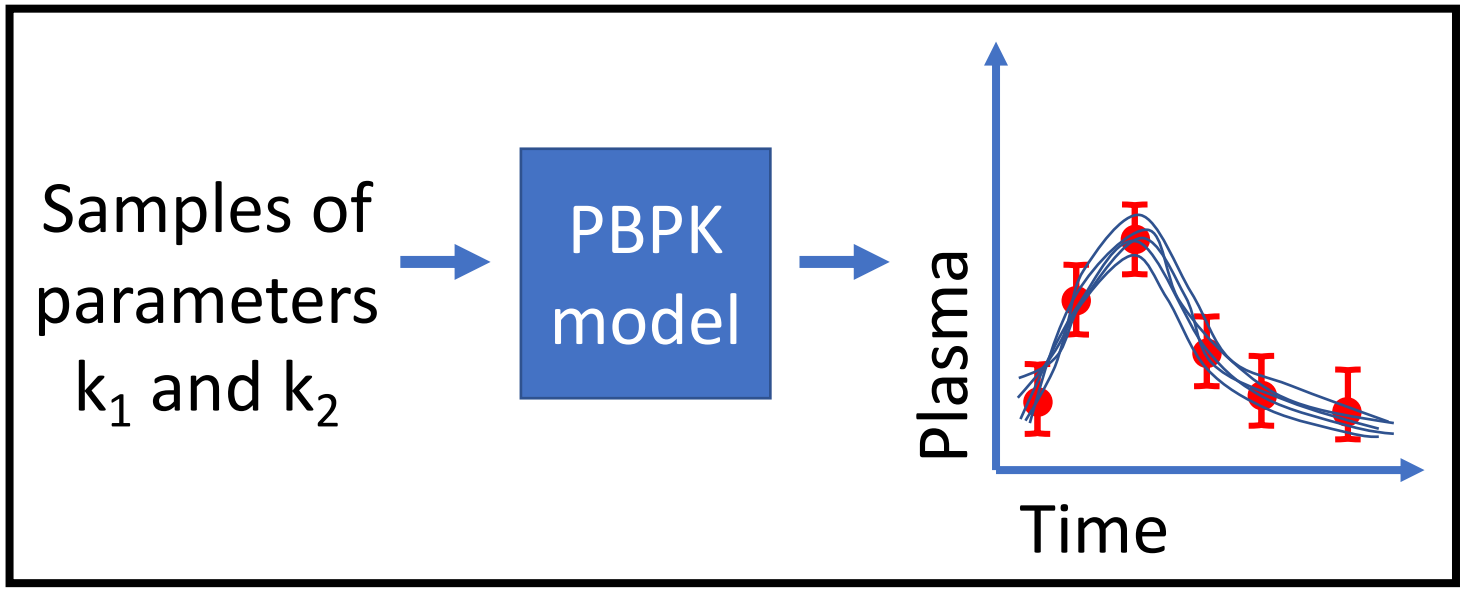
journal homepage: www.elsevier.com/locate/toxinvit

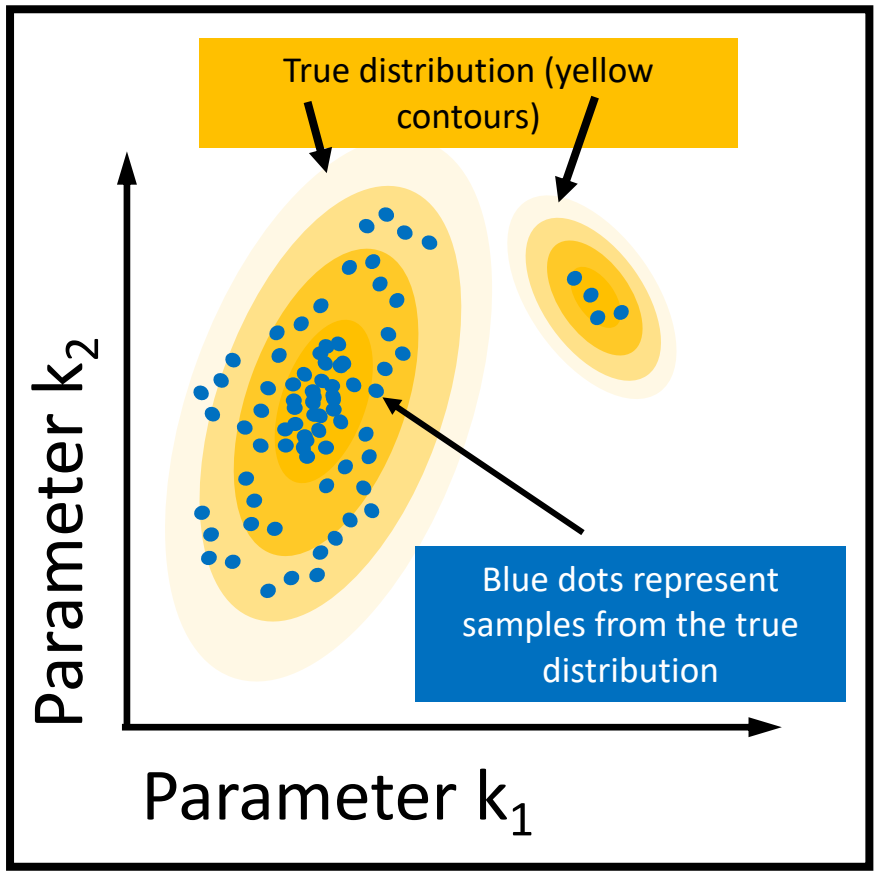
ELSEVIER

Partition coefficient and diffusion coefficient determinations of 50 compounds in human intact skin, isolated skin layers and isolated stratum corneum lipids

Corie A. Ellison[a,*], Kevin O. Tankersley[a], Cindy M. Obringer[a], Greg J. Carr[a], John Manwaring[a,1], Helga Rothe[b,2], Hélène Duplan[c], Camille Géniès[c], Sébastien Grégoire[d], Nicola J. Hewitt[e], Carine Jacques Jamin[c], Martina Klaric[e,3], Daniela Lange[f], Alexandra Rolaki[e], Andreas Schepky[f]

NONPARAMETRIC METHODS USED FOR MODEL TRAINING





- Sensitivity analysis reveals influential model parameters
- Influential parameters of mechanistic PK models may not be uniquely identifiable from experimental data.
- Complex correlations between parameters may not be expressible using parametric distributions.
- Nonparametric distributions represent probability density in parameter space numerically, may be determined using MCMC algorithms.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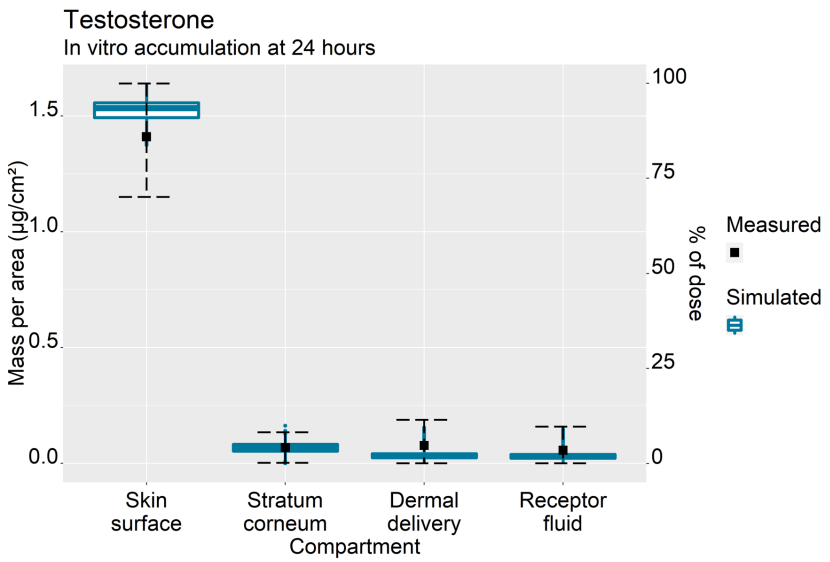
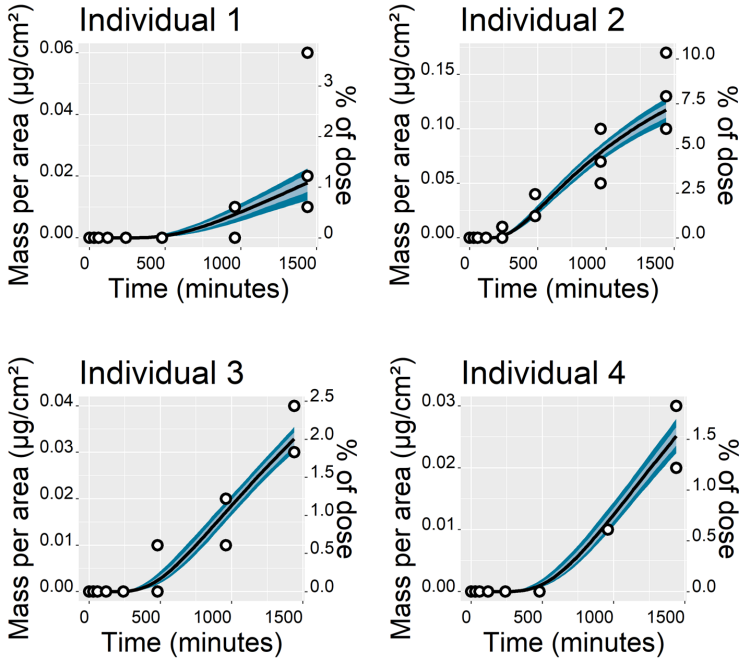
VISUAL PREDICTIVE CHECKS OF MODEL FITS TO IN VITRO DATA





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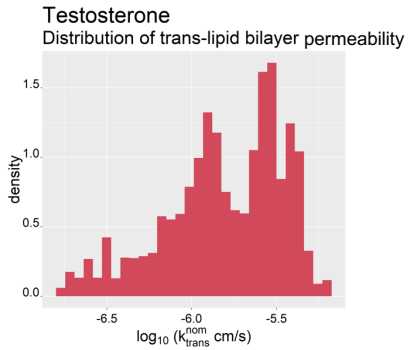
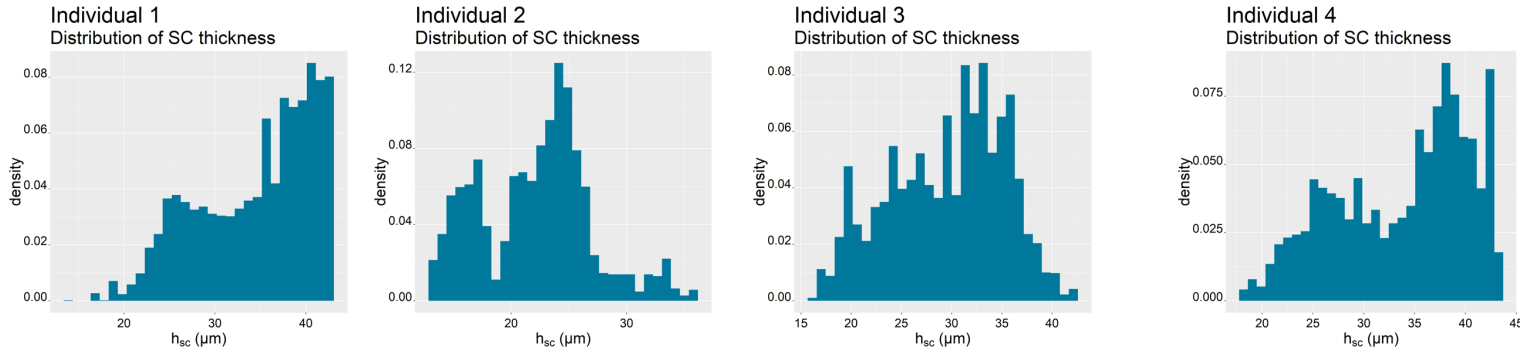
Learned compound-specific parameter distribution



Learned individual-specific parameter distribution



CONCLUSIONS

- There is increasing use and acceptance of model and simulation in submissions to regulators for dermal products.
- Model Master File reduces review time and unifies accepted science around a specific modeled scenario.
- Important features for an MMF to provide value: acceptance, availability, accessibility.
- Challenge: who has the incentive to build and share a MMF? Academic-industrial partnerships.
- Building a validated dermal MMF requires encompassing much detail:
  - skin permeation kinetics,
  - formulation effects
  - inter-individual variability
  - within-individual variability
  - inter-occasion variability