DERMAL ABSORPTION MODELING FOR *IN-VITRO* EXPERIMENTS USING HUMAN SKIN FOR FRAGRANCE CHEMICALS – APPROACH AND CHALLENGES

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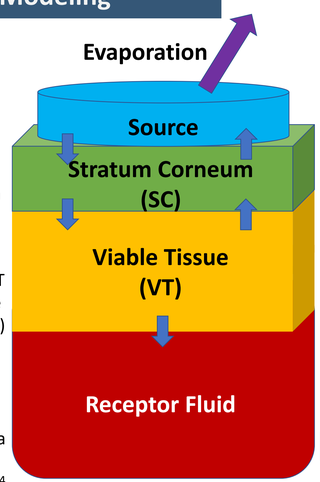
Model Overview

- The model consists of four well-mixed compartments in series that are each represented by an ordinary differential equation (ODE) with rate constants linking the compartments
  - Skin consists of two compartments representing the stratum corneum (SC) and viable tissue (VT), which includes the viable epidermis and some dermis
  - The source compartment describes chemical mass on the skin surface
    - Chemical absorbs into the SC and evaporates into air
    - Vehicle does not absorb into SC but evaporates into air
    - Exposed area is constant; decreased volume causes decreased thickness of the vehicle
  - Receptor fluid compartment, which is assumed to maintain sink conditions ($C \approx 0$)
- Rate constants between each compartment are estimated from permeability coefficients and thicknesses for the SC and VT (model B1 in reference 1 assuming mass transfer resistances in the source and receptor fluid compartments are negligible)
- Vehicle and chemical evaporation from the source compartment are represented by gas phase mass transfer coefficients (described in reference 2) that depend on molecular weight and vapor pressure
- Governing equations are solved numerically assuming initial concentrations in skin and receptor fluid are zero; this is done using the deSolve package in the R programming language

Experiments to Compare with Modeling

- Model results are compared with human skin *in vitro* permeation (IVPT) data from Hewitt et al.[3] for non-occluded finite dose exposures to 26 chemicals for 24 h
  - Abdominal skin from surgical waste dermatomed (~400 μm) and frozen until used (3 replicates from each of 4 donors)
  - Chemical was applied in 10 μL/cm^2 of an aqueous solution (phosphate buffered saline; PBS) at selected concentration to 1 cm^2 skin area
  - Experiments were maintained at 32° C
- Model rate constants are calculated using experimental permeability data for SC and dermis (assumed to equal VT permeability) reported by Ellison *et al.*[4] from infinite dose IVPT experiments with human cadaver skin (back or thigh) treated with a proprietary freezing media (containing glycerin, buffer and DMSO) and frozen until used; assumed thickness of SC (25 μm) and VT (375 μm)
- 30 chemicals from Hewitt et al. [3] were excluded because the vehicle was not PBS, experiments were conducted in a fume hood (which may have affected evaporation rates) or permeability data were not available from Ellison *et al.*[4]



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Surface Dynamics

Depending on the vehicle, its properties, and the timescale of the exposure, the vehicle may evaporate during an exposure, leaving a film of neat chemical on the SC surface, assumed to completely cover the exposed area for the exposure time (or until all chemical is gone). The dynamics of chemical absorption and permeation after the vehicle is gone will vary. We consider two scenarios for the film of neat chemical.

Vehicle evaporation time

The aqueous vehicle (10 μL/cm^2 of PBS) is estimated to completely evaporate in 6.5 min (based on a gas phase mass transfer coefficient of 0.41 m/h, calculated as described in reference 2 for 10 cm/s air velocity, 1 cm path length, and 0.25 cm^2/s water diffusivity in air)

Scenario 1 (chemical absorption continues):

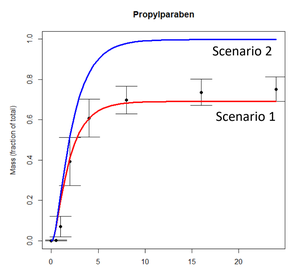
- Chemical continues to absorb into the SC and evaporate into air
- Rate of absorption into SC and evaporation are the same as from the saturated vehicle (which has the same thermodynamic driving force as neat chemical)
- We expect this scenario to model behavior of a liquid film of neat chemical; it may also model behavior of a film of solid chemical with significant vapor pressure

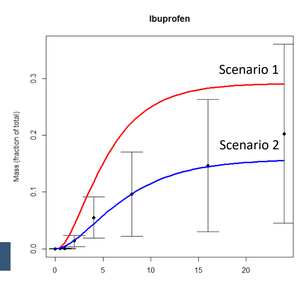
Scenario 2 (chemical absorption stops):

- Chemical absorption into and out of the SC stops
- Chemical evaporation into air continues
- We expect this scenario to model the behavior of a solid film of neat chemical at skin temperature

Cumulative Mass Predictions

- Plots presented below compare experimental data for cumulative mass of two chemicals versus time (points and error bars designate means and ± 1 standard deviation) with model predictions of the two scenarios that exhibit different behavior.
  - For ibuprofen, Scenario 1 > Scenario 2 because chemical is present in the source compartment for the entire 24 h; therefore, for Scenario 1 absorption into the SC occurs for the entire 24 h
  - For propylparaben, Scenario 2 > Scenario 1 because chemical is completely depleted from the source compartment before the aqueous vehicle has evaporated (i.e., in <6.5 min). After this, for Scenario 1, some chemical that has absorbed into the SC can evaporate into the air, reducing chemical transfer to the receptor
- In comparisons of predictions and data for cumulative mass in the receptor fluid at 24 h, one of the two scenarios deviates from the data
  - By < an order of magnitude for 22 chemicals
  - By < a factor of 2 for 14 chemicals
- Preliminary comparisons of the best scenario for each chemical with melting point and vapor pressure do not demonstrate the expected correlation. Factors that may contribute to this lack of correlation include:
  - Permeability was measured in skin treated with solution containing glycerin and DMSO whereas skin in the finite dose experiments was not
  - Input parameter variability is not considered
- Other limitations of the model include:
  - Ionization was not considered
  - Binding or reactions in either the SC or VT were not considered





References

1) McCarley KD, Bunge AL, Physiologically relevant two-compartment models for skin, *J Pharm Sci*, **89**:1212-1235.
2) Frasch HF, Bunge AL, The transient dermal exposure II: Post-exposure absorption and evaporation of volatile compoun *Pharm Sci,* 104:1499-1507 (2015).
3) Hewitt NJ *et al.* Measurement of the penetration of 56 cosmetic relevant chemicals into and through human skin using a standardized protocol. *J Appl Toxicol* **40,** 403–415 (2019).
4) Ellison CA *et* al. Partition coefficient and diffusion coefficient determinations of 50 compounds in human intact skin, isolated skin layers and isolated stratum corneum lipids, *Toxicol In Vitro*, **69**:104990 (2020).

Predicted Chemical Mass Fraction in the Compartments

- Model predictions of the chemical mass fraction in each compartment over time show how the chemical moves through the system; see example plots below
- Propylparaben is completely gone from the source compartment before the vehicle evaporates. After this, Scenario 1 predicts that about 31% of the chemical in the skin evaporates; the remainder permeates through the VT to the receptor fluid.
- Predictions for both scenarios are presented for cyclophosphamide monohydrate (below).
  - Only 3.8% of the initial mass absorbed into the SC in the first 6.5 min while the vehicle is present
  - If absorption into the SC continues (Scenario 1) the mass fraction of chemical in the SC increases until the chemical is depleted from the source compartment by absorption and evaporation, which causes the mass fraction in the SC to decline
  - If absorption into the SC stops, then the mass fraction of chemical in the SC decreases as chemical moves through the VT to the receptor fluid; chemical continues to evaporate from the neat chemical film
  - This chemical is a solid at skin temperature; consistent with this, Scenario 2 provided a better prediction of the experimental cumulative mass in the receptor fluid