# Dermal Absorption Model

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# Outline

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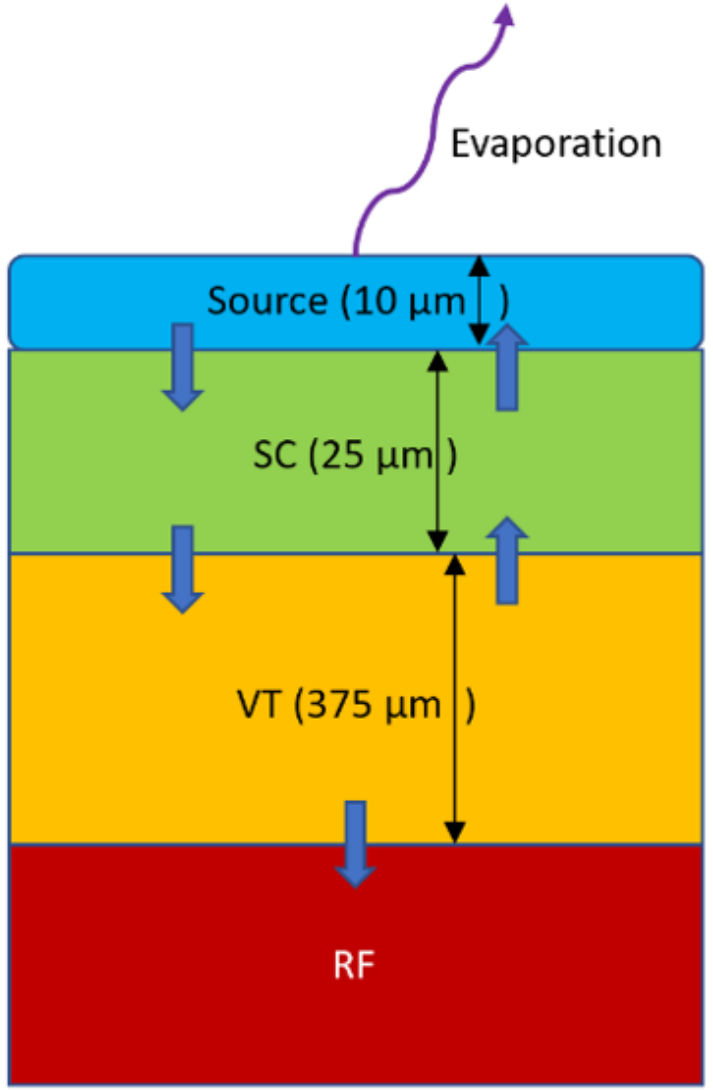
# Model Overview

- 4 compartment in vitro model:
  - Source: vehicle and chemical on the surface of the skin
  - SC: stratum corneum
  - VT: viable tissue; combination of viable epidermis and dermis
  - RF: Receptor Fluid
- Chemical mass flows between compartments
  - Well-mixed (ODE) Model
  - Rate constants set to approximate a Diffusion (PDE) Model
- Receptor Fluid maintains sink conditions
  - This matches experimental set-ups, not real systems
  - Must incorporate blood flow rate to determine the 'back flow' for real systems



# Finite Vehicle

- One assumption of the original model that does not align with practical situations was that of constant vehicle volume
- We now calculate the rate at which the vehicle evaporates, assuming a thin film of water, and incorporate this
- This introduces the issue of modeling the remaining chemical if the vehicle evaporates too fast
  - The response to this issue will need to vary based on the chemical being modeled

Evaporation rate, of both vehicle and chemical, is proportional to gas phase mass transfer rate:

$$k_g = 3260 * D^{\frac{2}{3}} * \left(\frac{v}{A_{sk}^{0.5}}\right)^{0.5}$$

Where

$$D = 10^{-3} * \frac{T^{1.75}}{P * \left[(V)^{\frac{1}{3}} + (V_{air})^{\frac{1}{3}}\right]^2} * \left(\frac{MW + MW_{air}}{MW * MW_{air}}\right)^{0.5}$$

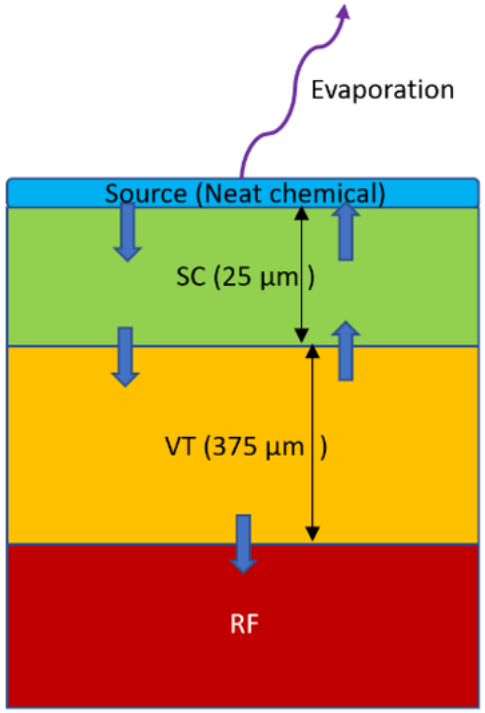
Note: $v$ above is the ambient air velocity, a value that can vary significantly based on the situation and is not commonly measured

Other Parameters:

$A_{sk}$= exposure area
T = Temperature
P = pressure
MW = molecular weight of chemical
$MW_{air}$= molecular weight of air
V = diffusion volume of chemical
$V_{air}$= diffusion volume of air

# Post - Vehicle Scenarios

## 1: Liquid Chemical

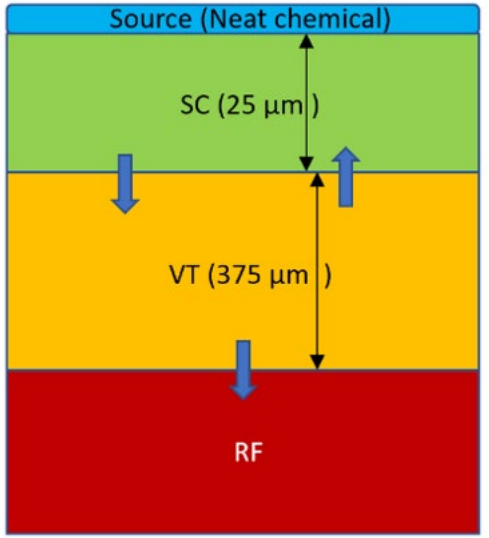



Once the vehicle has evaporated, we look at 2 different methods for modeling any remaining neat chemical:

1) Chemical is a liquid (left)
   - Assumed dynamics as if a fully saturated aqueous vehicle present
2) Chemical is a solid (right)
   - Assumed no flux across the upper layer of skin, in or out
   - Dynamics within the skin unaffected

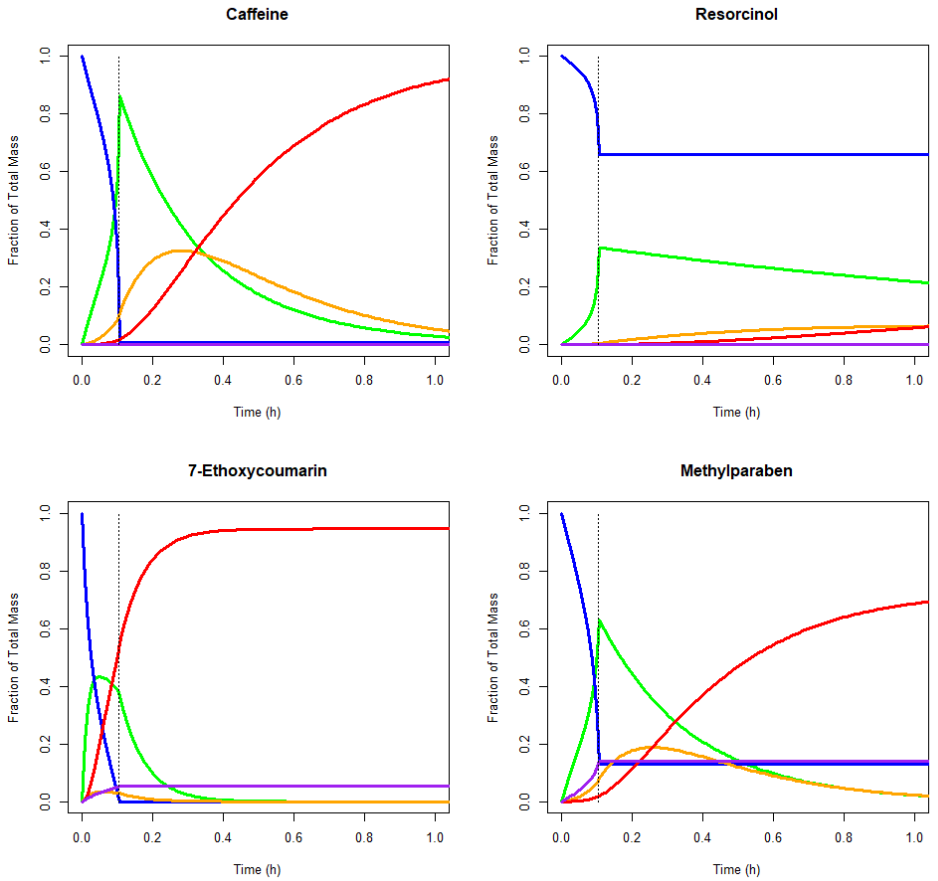
These were chosen as initial test scenarios. They are not expected to fit all chemicals, but more will be proposed after further study

## 2: Solid Chemical



# Compartment-wise Chemical Mass

- Model outputs include time-course data for the chemical concentration in each compartment over time
  - Only showing 1st hour of 24; equilibrium is reached soon after
- 4 sample chemicals shown to the right
  - Right two show leftover chemical on the surface (both chemicals are solid at skin temperature)
  - Top two show little evaporated chemical mass; bottom two have noticeable evaporation but <20% of the total mass




Fraction of chemical in:

Red = Receptor Fluid

Blue = Source

Green = Stratum Corneum

Orange = Viable Tissue

Purple = Evaporation Mass

# Experimental References

## Input Parameters (Ellison)

- Used measured values for permeabilities taken by Ellison et al.
  - 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)

## Time Course Comparison (Hewitt)

- Compared predictions of the model to measured values from Hewitt et al.
  - 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$^o$ C

References:

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).

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).

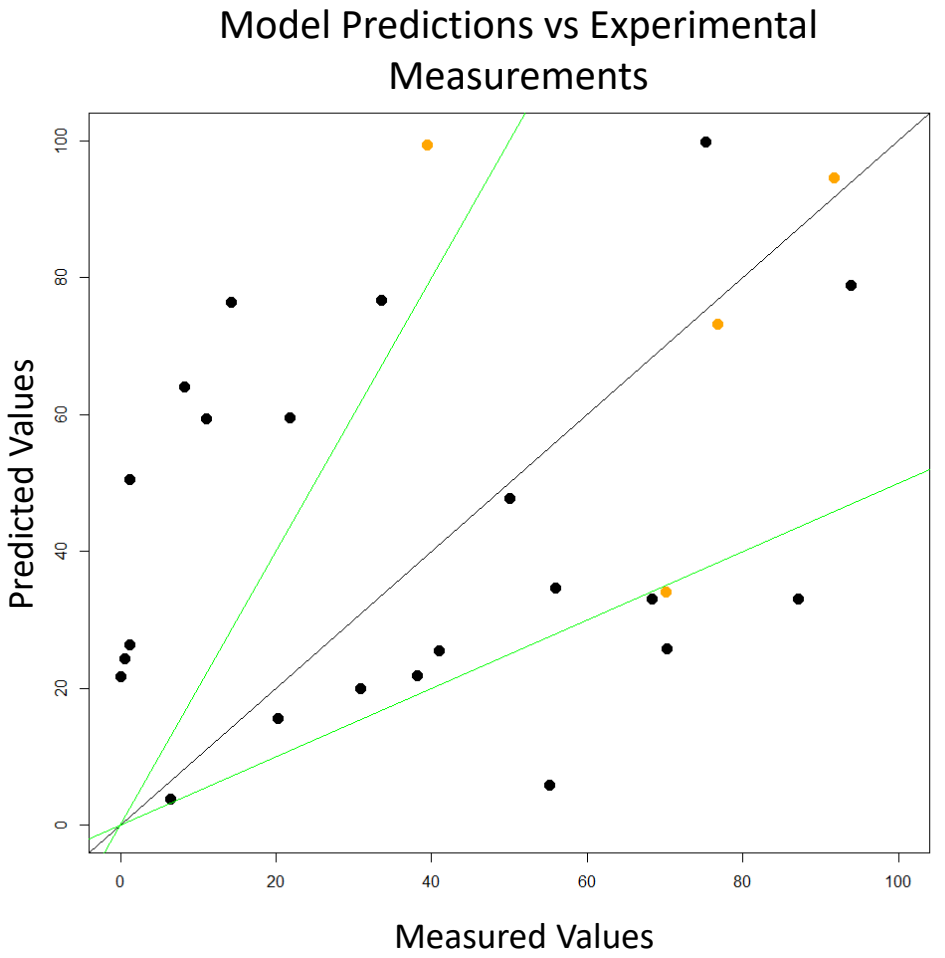
# Validating Outputs

- Initially filtered Hewitt's 50 chemical dataset to 26 using following criteria:
  - No fume hood used
  - PBS vehicle; not ethanol
  - Chemical also measured in Ellison
- Values for these 26 chemicals were gathered:
  - Permeability values taken from Ellison
  - Chemical parameters (mw, logkow, etc) taken from Comptox

- Ran the model for each chemical using these parameters, matching experimental prameters to Hewitt's where possible:
  - 24-hour exposure window
  - 10 $\mu L/cm^2$ of vehicle
  - Initial chemical concentration varied by chemical
  - Skin compartment thickness based on measurements
- Compared percent of total mass absorbed into receptor fluid at 24-hours between Hewitt's measurements and our predictions

# Data vs Predictions

- We look at mass, as a percent of the total, in the receptor fluid after 24 hours
  - X axis is Measured Data (Hewitt)
  - Y axis shows model prediction
- Black line shows x=y line
  - Green lines show ‘factor of 2’
- Orange dots show 4 previously presented chemicals

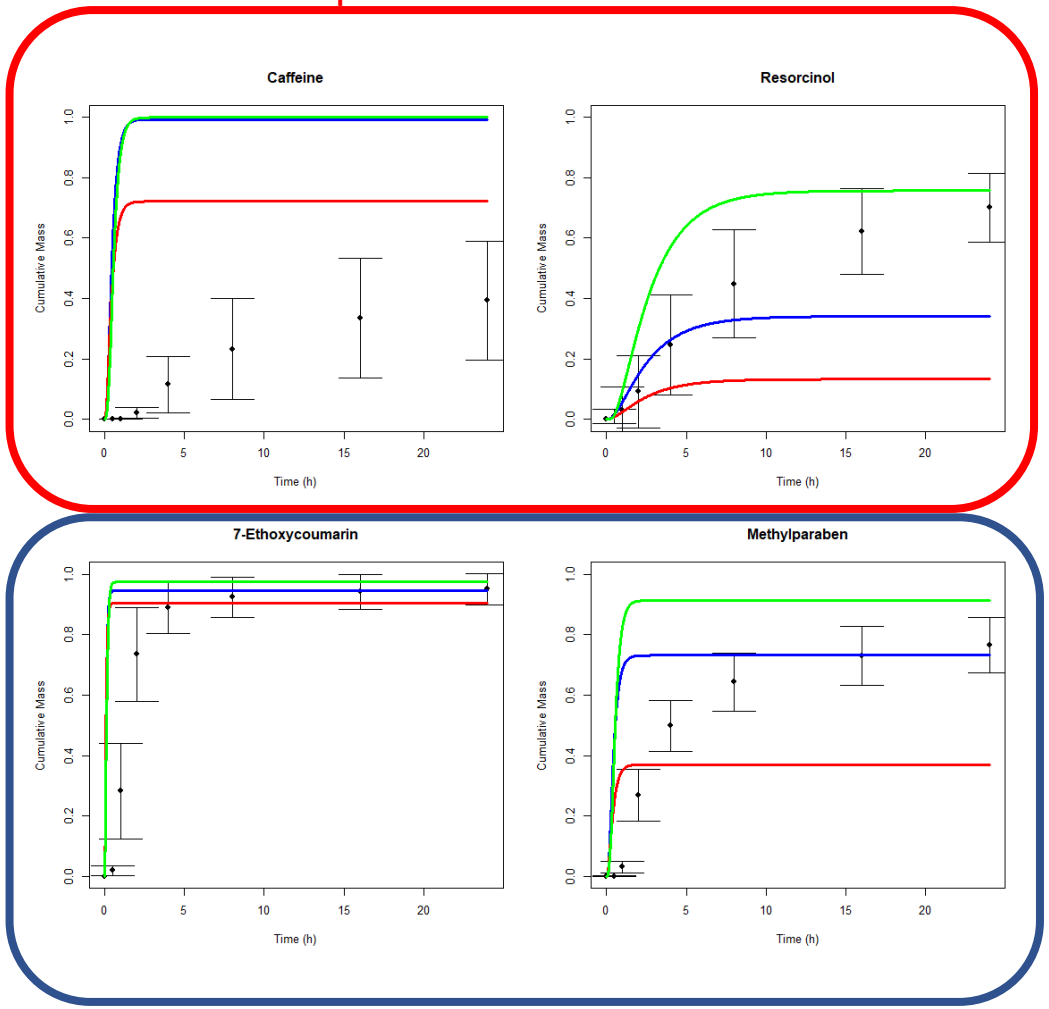



- Of the 26 chemicals:
  - 10 overestimate by > 2x (including Caffeine)
  - 5 underestimate by > 2x (including Resorcinol)
  - 11 are within the range

# Uncertainty from Ambient Air Velocity

- We found that ambient air velocity plays an important role in the model
  - Evaporation rate is proportional to the square root of this velocity
  - It is rarely measured and can differ by orders of magnitude (1.1 – 80 cm/s, with 10 cm/s as a reasonable default value)
- Left two chemicals show the least change with air velocity
  - These are the two that do not leave neat chemical after vehicle evaporation
  - Model is most sensitive to air velocity when vehicle evaporation is fast enough that chemical reaches a saturation concentration
    - This happens for caffeine at v = 80 cm/s, but not for v = 10 cm/s
    - The slight differences for 7-Ethoxycoumarin are primarily due to chemical evaporation; faster evaporation will cause less absorption
  - Top two had little to no chemical evaporation, so any difference is due to vehicle evaporation

Low evaporation




High evaporation

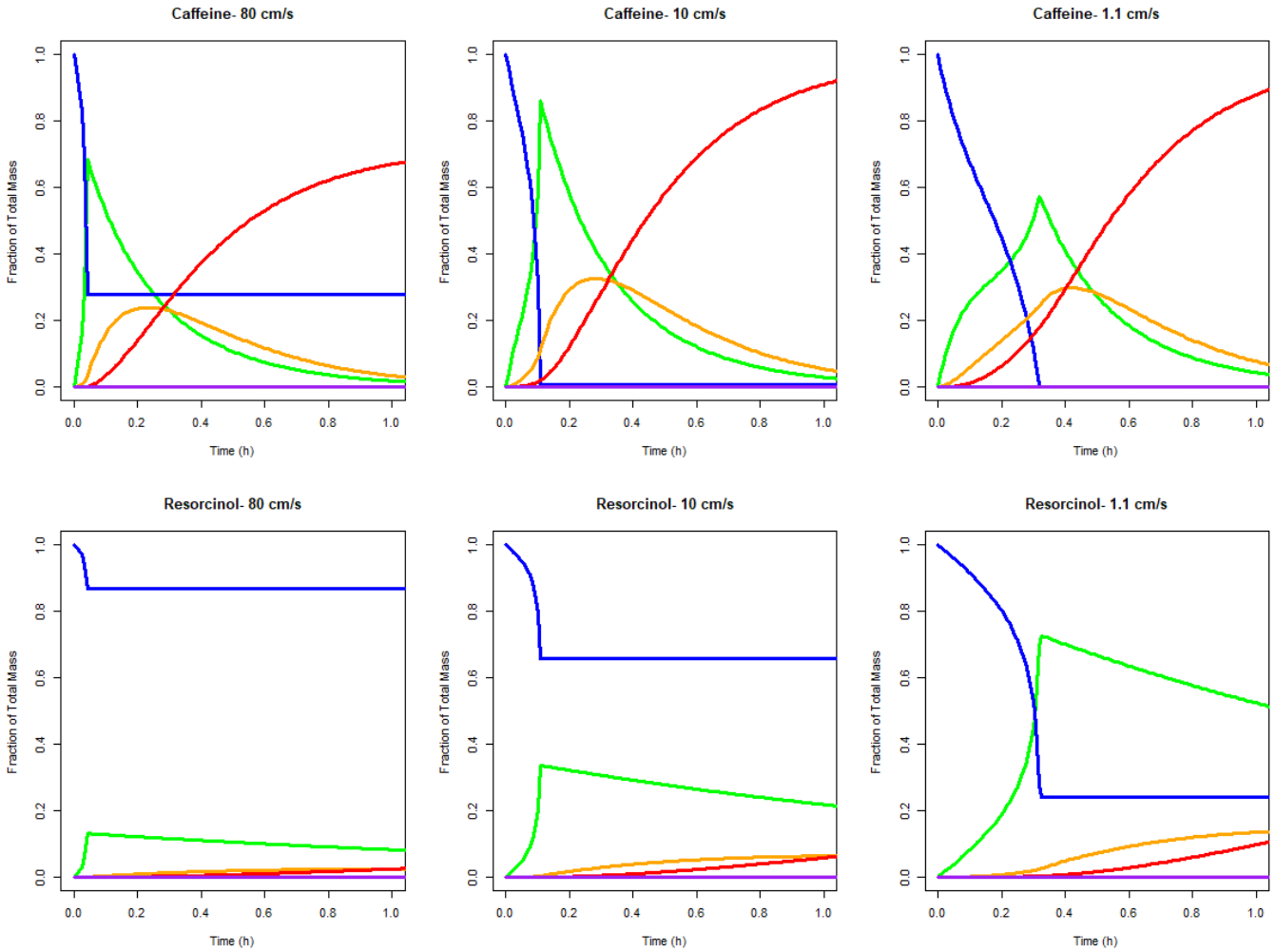
Red:
V = 80 cm/s

Blue:
V = 10 cm/s

Green:
V = 1.1 cm/s

# Effect of Air Velocity on Outputs (Chemicals with low Evaporation)

- Lower velocity slows evaporation of vehicle
  - Chemical has longer to absorb
  - Vehicle reaches saturation concentration slower
- Largest effect on model is when chemical does not have time to fully absorb
  - Predictably, giving it more time to absorb has a significant effect
  - If it all will be absorbed for both velocities, velocity changes the timing and rate of absorption more than the total absorption




Red = Receptor Fluid

Blue = Source

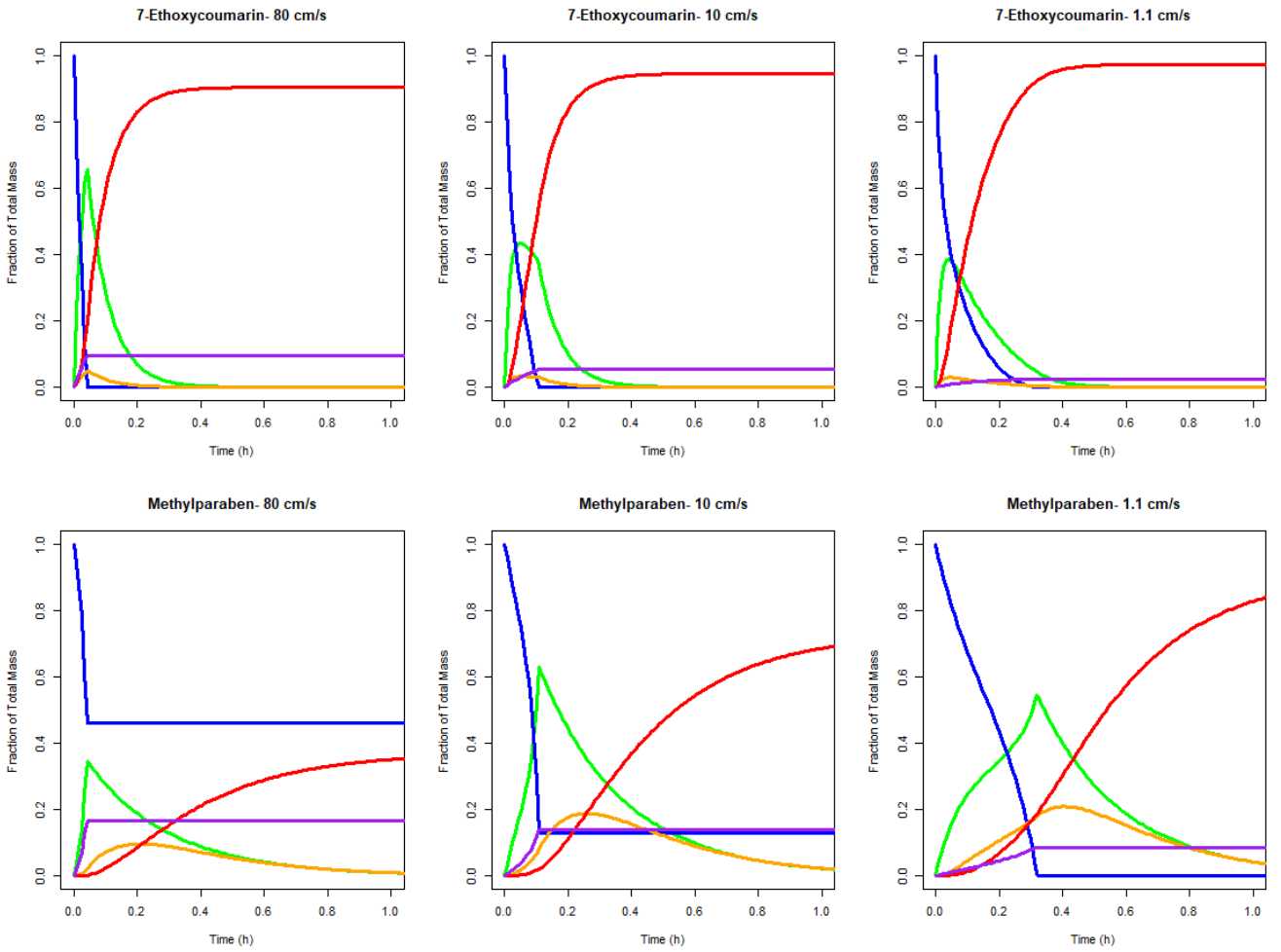
Green = Stratum Corneum

Orange = Viable Tissue

Purple = Evaporation Mass

# Effect of Air Velocity on Outputs (Chemicals with high Evaporation)

- 7-Ethoxycoumarin's evaporation is responsible for most of the difference in the top three plots
  - Because it evaporates faster than the vehicle, it does not reach a saturation concentration in any case
  - Primary dynamic is the rate of absorption into sc vs rate of evaporation
- Methylparaben is left over after vehicle evaporation for all but the v = 1.1 cm/s case
  - Reduction in total amount evaporated is less significant than for 7-Ethoxycoumarin
    - Evaporation is slower but happens for a longer period for lower v values

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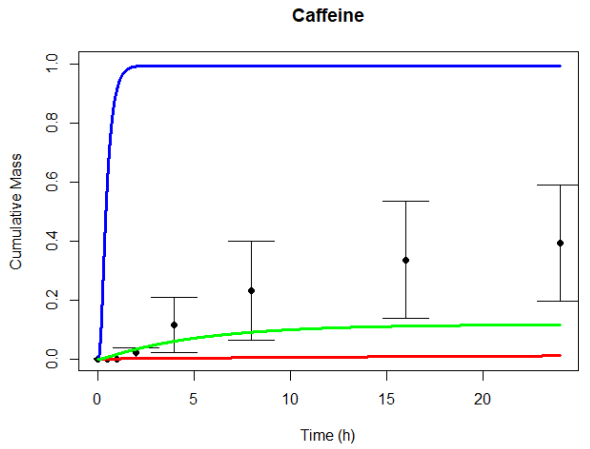
# Uncertainty Permeability

Each colored curve the model run for the chemical using a different experimentally measured Kp value:

Blue: Ellison Kp
Green: High Rothe Kp
Red: low Rothe Kp

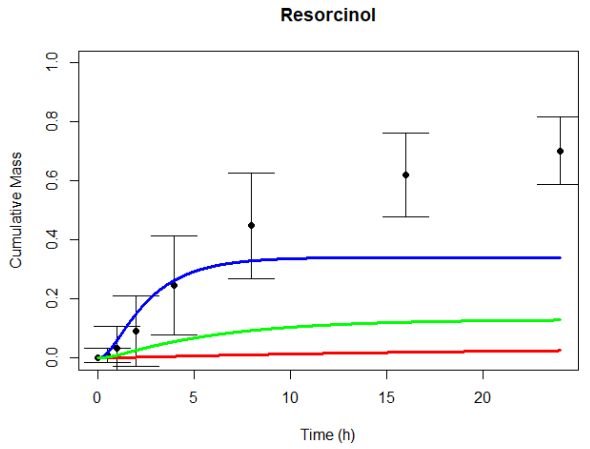
- Permeability (Kp) also varies from experiment to experiment
  - Rothe et al. measured Kp for caffeine and resorcinol that differed from Ellison's measurements
- To demonstrate the significance of reasonable variations in Kp, we ran the model using the Ksc (permeability in the sc) values from Ellison and compared them to model runs using Rothe's Ksc values
  - As Rothe presented standard deviations, we used the measured mean plus and minus 1 sd for comparison
  - Only 1 permeability value was changed (Ksc) to isolate any differences
    - Ksc was selected because sc is typically the compartment that slows absorption the most
- This exercise attempts to visualize model uncertainty introduced by Ksc input uncertainty from:
  - Two different experimental measurements
  - Measurements from within a single experiment




Red:
Kp = $1.56 \times 10^{-4}$ cm/h

Blue:
Kp = $2.5 \times 10^{-2}$ cm/h

Green:
Kp = $9.56 \times 10^{-4}$ cm/h




Red:
Kp = $3.6 \times 10^{-4}$ cm/h

Blue:
Kp = $3.8 \times 10^{-3}$ cm/h

Green:
Kp = $1.32 \times 10^{-3}$ cm/h

Ellison permeability values compared to those found in:

Rothe, H., et al. (2017). "Comparison of protocols measuring diffusion and partition coefficients in the stratum corneum." Journal of Applied Toxicology **37**(7): 806-816.

# Closing Remarks

- The model can predict chemical uptake for a wide range of chemicals and situations
  - We do not yet know for which groups of chemicals these predictions are useful
  - Permeability is an important input, but varies across experiments for some chemicals
  - Ambient air velocity is also important but rarely measured
- We suspect some dynamics that are neglected (binding, chemical reactions) could be significant in some circumstances and hope that studying the chemicals that are not predicted well will highlight which of these are most important and for which chemical groups these additions are necessary