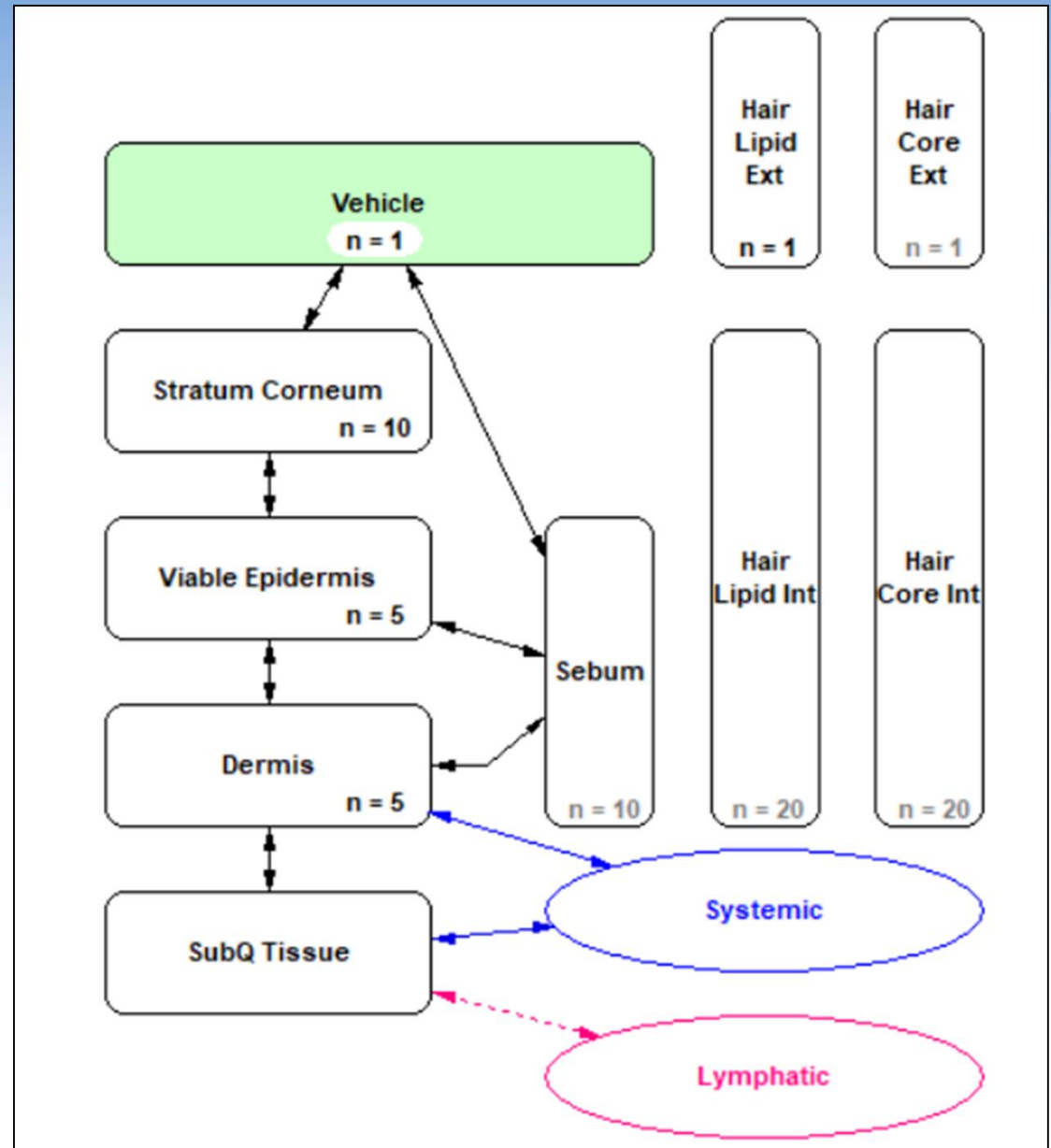


# ***In Silico-In Vitro* Extrapolation for Dermal Exposure**

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Simulations Plus, Inc.

# *In silico* modeling of dermal exposure

- The TCAT™ module within GastroPlus was originally developed to predict drug disposition *in vivo* after topical or subcutaneous application
- Since this is a mechanistic model, we thought it should also be able to model *in vitro* exposure
- We also wanted to do further validation of the model and identify areas that can be improved



# Cosmetics Europe *in vitro* measurements of dermal exposure

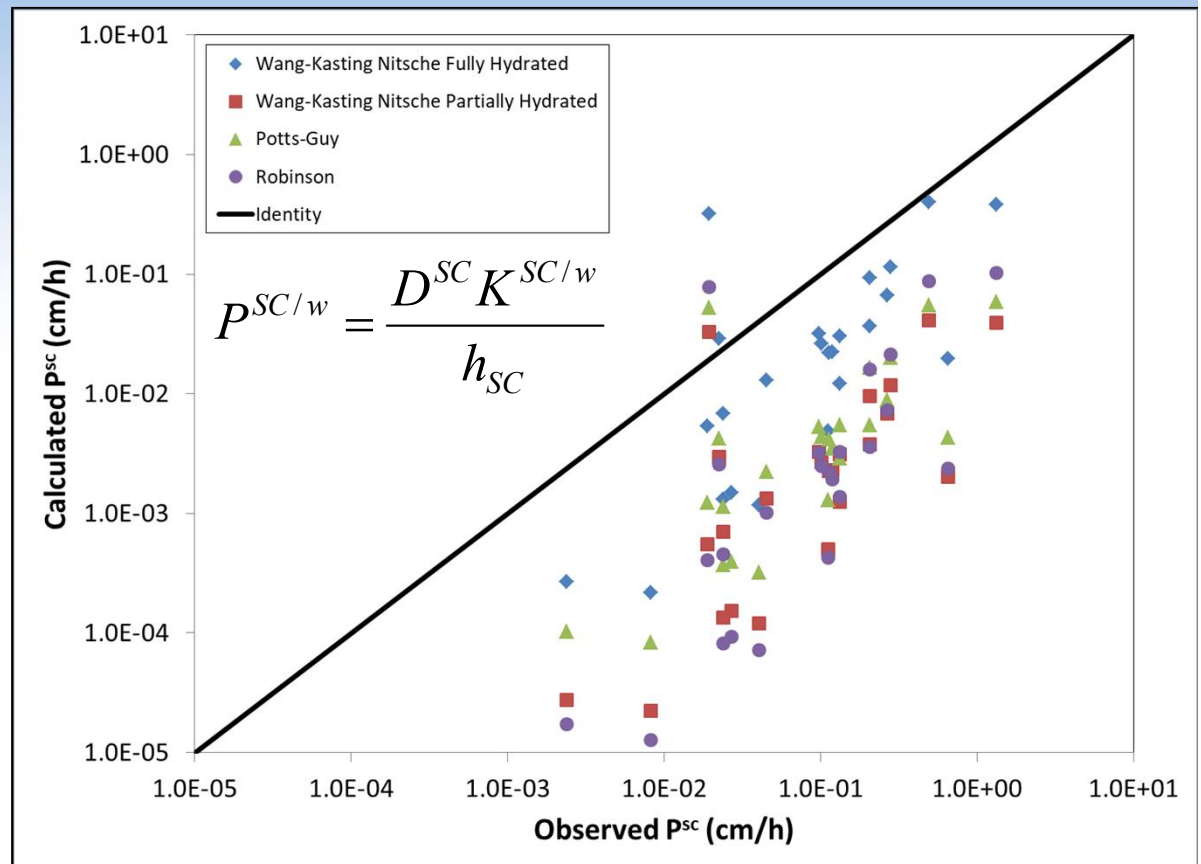
- 25 compounds were administered *in vitro* in flow-through diffusion cells to human abdominal skin
- Most compounds delivered in 0.1 or 0.01 M phosphate-buffered saline
  - Three compounds were delivered in PBS and ethanol, and one compound was delivered only in ethanol
- Physicochemical properties were provided for each compound
- Diffusivity ( $D^{sc}$ ) and stratum corneum/buffer partition coefficient ( $K^{sc/buffer}$ ) were provided for all compounds

# Stratum corneum permeability models

- **Wang-Kasting-Nitsche** (Wang et al, *J Pharm Sci*, 2007)
  - Most mechanistic model
  - Includes models for **fully** and **partially hydrated** skin—fully hydrated is expected to describe *in vitro* conditions, and partially hydrated to describe *in vivo* conditions
- **Potts-Guy** (Potts and Guy, *Pharm Res*, 1992)
  - Correlation based on logP and MW
- **Robinson** (1993) – P&G internal model (Wilschut, *Chemosphere*, 1995)
  - Considers contributions of different parts of stratum corneum to permeability
- How well do the permeability predictions from these models compare to measured values?

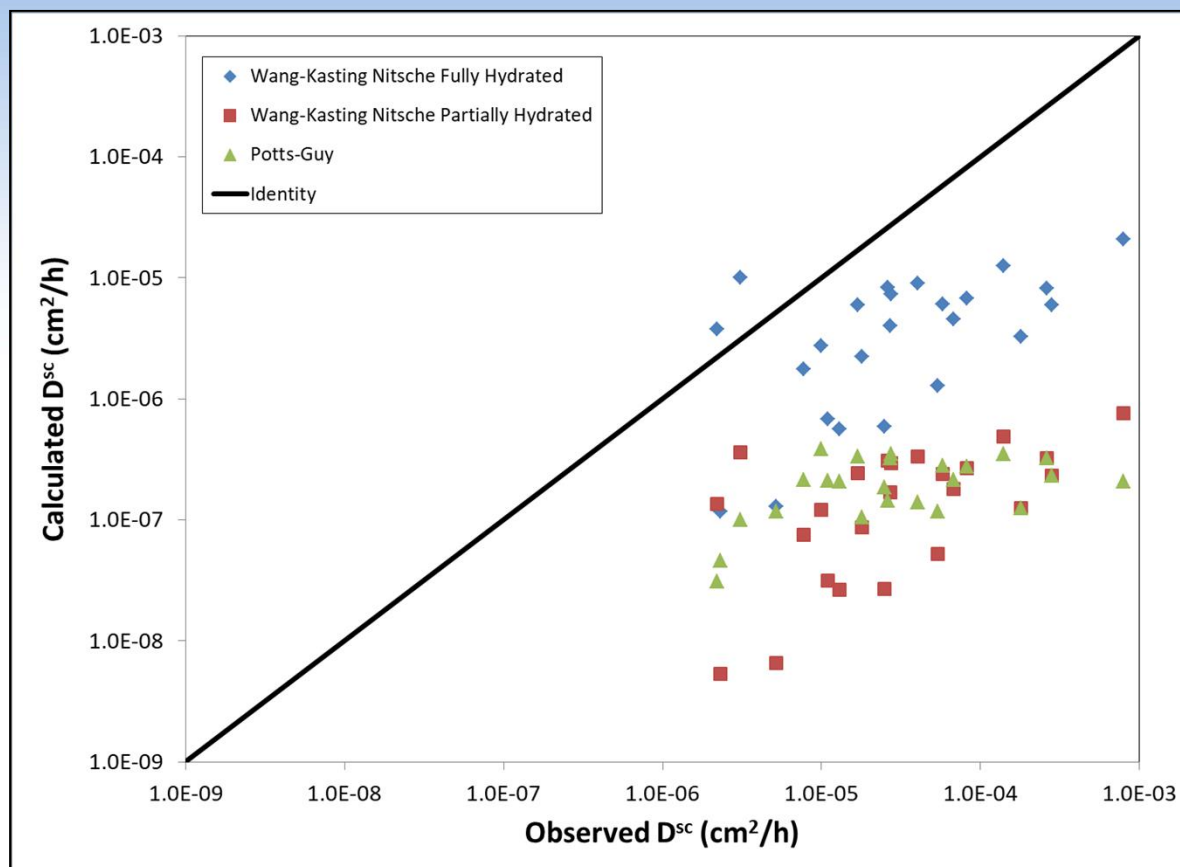
# Stratum corneum permeability: Predicted vs. measured

- All predictive models tended to underpredict observed permeability values
- The WKN fully hydrated model was closest to the identity line



# Stratum corneum diffusivity: Predicted vs. measured

- Diffusivity in stratum corneum is consistently underestimated by ~100-fold by all methods
- WKN fully hydrated model comes closest to measured values



# Differences in experimental conditions may explain disparity

Example Compound	CosEu measured value	Flynn dataset (1990)
Permeability (cm/h)	2.32e-2	2.4e-4

The remaining 123 experimental permeation coefficients can be distinguished on basis of exposure conditions like temperature, duration of contact, concentration and the type of skin. The anatomical location from which the human skin was derived, was unknown for 29 permeation coefficients. Temperature maintained in the experiments approximated a skin temperature of 32°C. Mean temperature for 115 *in vitro* experiments was 30°C. Three kinds of diffusion cells were used, dependent on the extent of active mixing of the receptor fluid. Mostly, the receptor medium was static or stirred (n=121). Only, two permeation coefficients were measured in a flow-through diffusion cell with a flow of 5 ml/hour. Besides the kind of diffusion cell used, the receptor medium itself can influence the skin permeation *in vitro*. Depending on the solubility of a compound in the receptor medium and the concentration gradient across the skin, skin permeation will be enhanced or slowed down. In 15 percent of the *in vitro* studies, the receptor medium was unknown. An aqueous solution was often used. Other receptors used in these studies were phosphate buffers and saline. These differences in experimental settings are not taken into account in the model fitting in spite of the influence they might have on the outcome of that fitting.

- Wilschut et al, *Chemosphere*, 1995

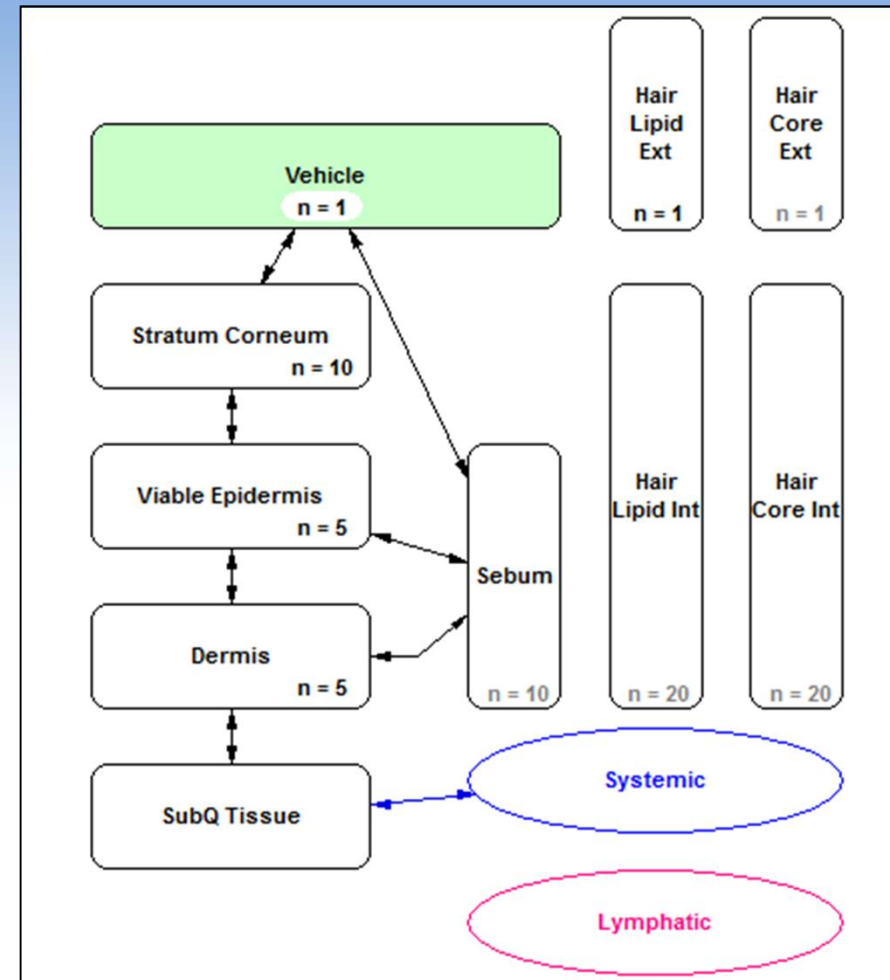
# Simulating in vitro conditions: vehicle

- All dose administration is modeled as “TD: Solution” in GastroPlus™
- PBS vehicles are modeled as water
- Vehicle evaporation is predicted according to the Nielsen equation (Nielsen et al, *Ann Occup Hyg*, 1995)
  - Assumption that PBS and ethanol vehicles will fully evaporate, and that no absorption can occur after vehicle evaporation
- Compound evaporation is modeled by removing the reported percent evaporated from the initial dose

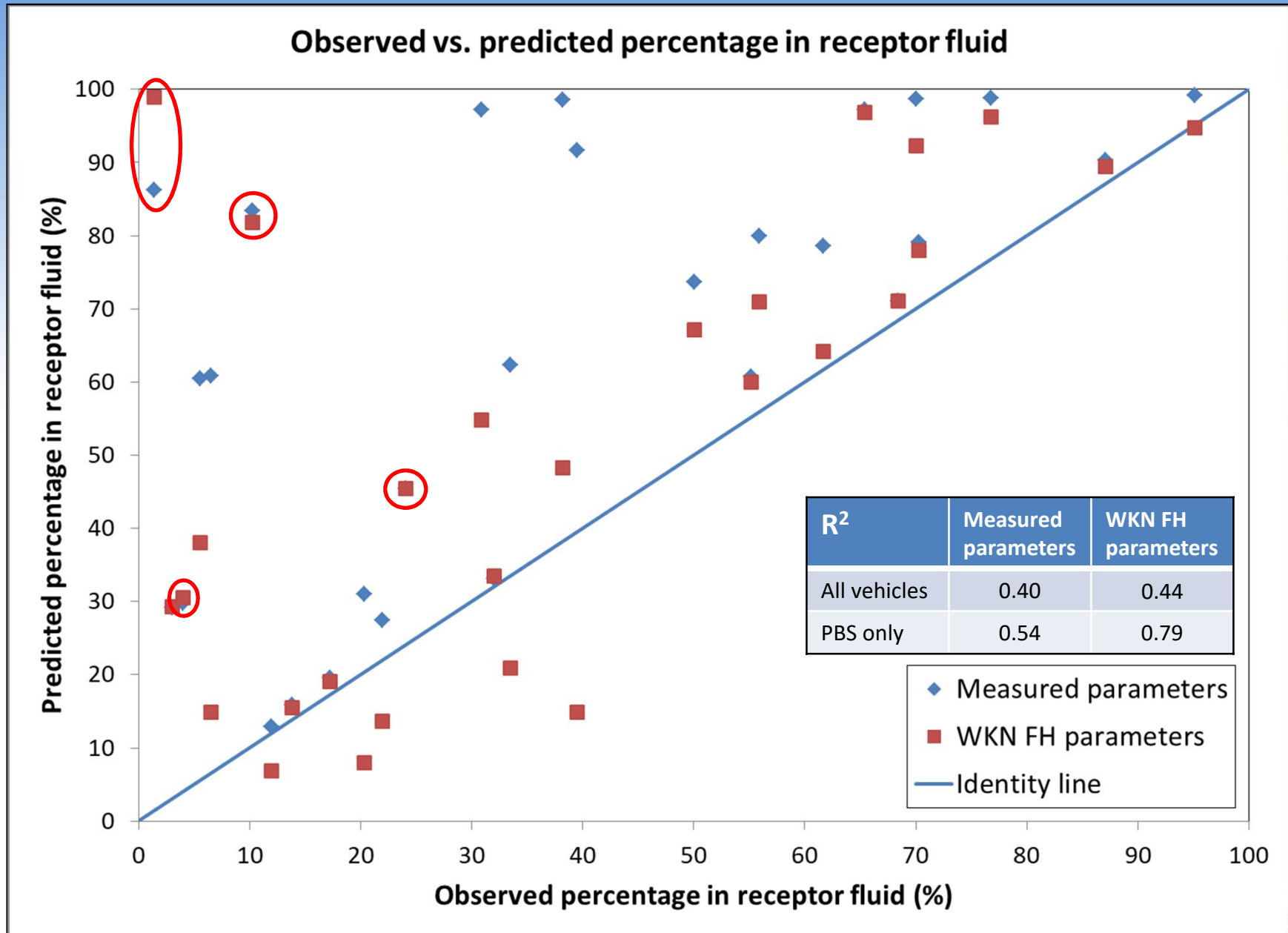


# Simulating in vitro conditions: skin

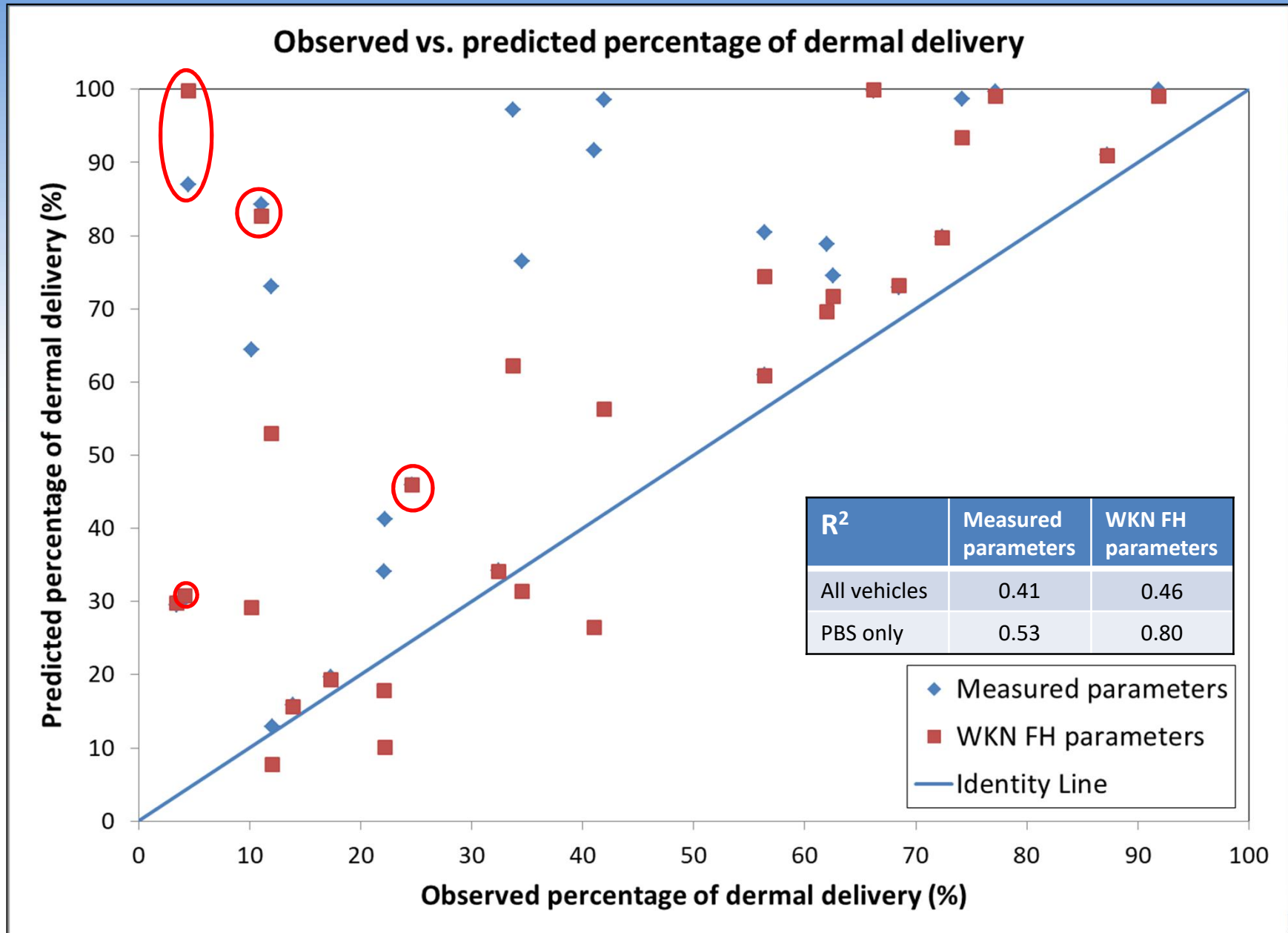
- Human-abdomen skin physiology
- Stratum corneum permeability is modeled using measured values and WKN fully hydrated model
- Viable epidermis and dermis permeability are modeled using Kretsos equation (Kretsos et al, *Int J Pharm*, 2008)
- Sebum is modeled using equations derived from Valiveti (Valiveti and Lu, *Int J Pharm*, 2008; Valiveti et al, *Int J Pharm*, 2009)
- Dermis thickness is calculated according to reported skin thickness
- Subcutaneous tissue is modeled with properties similar to water, blood flow equivalent to flow in diffusion cell (1 ml/h)



# Receptor fluid, Nielsen evaporation



# Dermal delivery, Nielsen evaporation



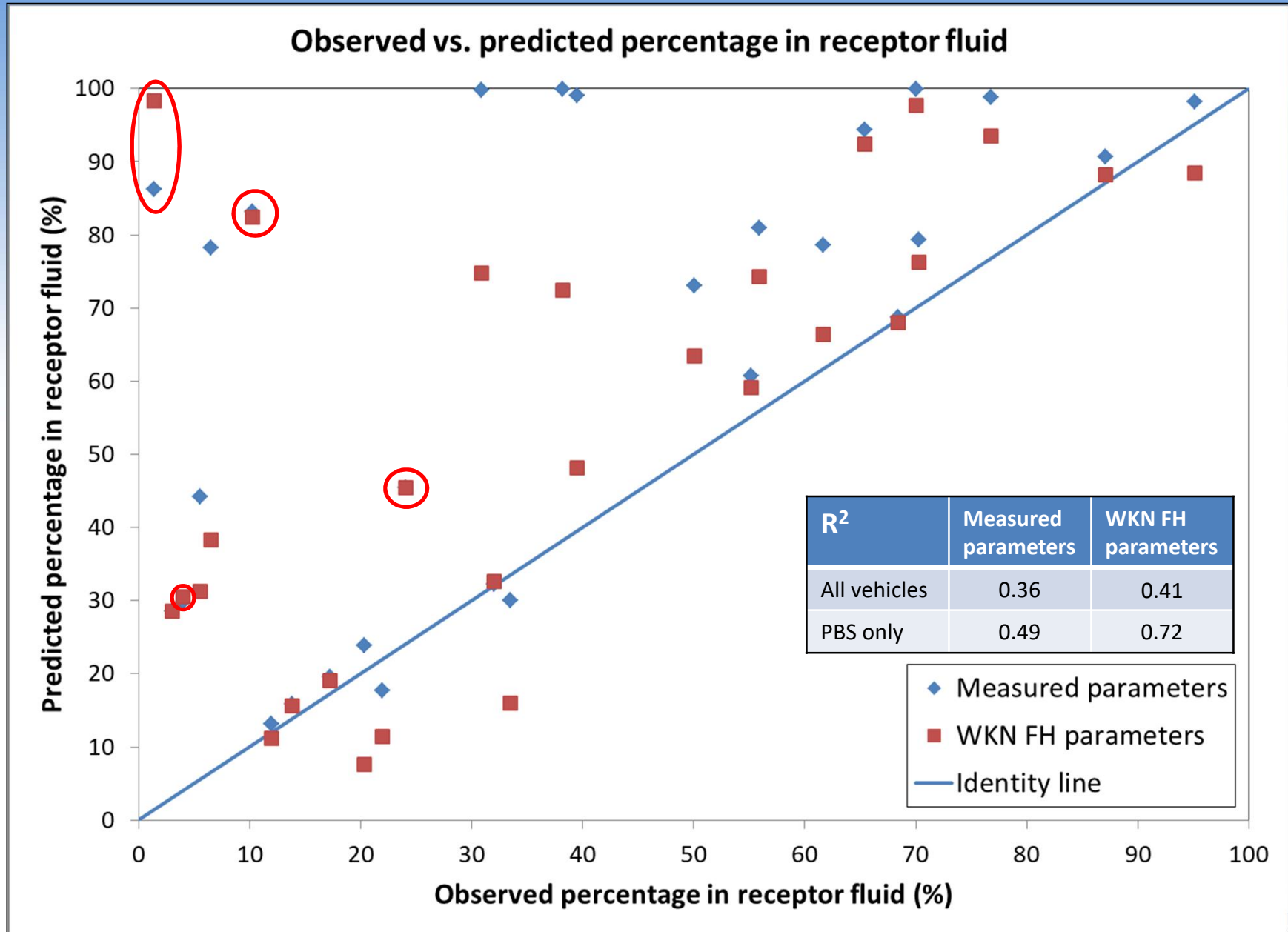
# Results of initial simulations

- Simulations using WKN predicted permeability for stratum corneum are more accurate than using the measured permeability parameters
- Both measured and WKN predicted parameters for stratum corneum permeability tend to overestimate the experimental data
- This modeling approach is not able to predict administration from an ethanol vehicle very well

# Effect of vehicle evaporation

- There are several different models of vehicle evaporation included within the TCAT™ module
- The default is the Nielsen model, which predicts the shortest evaporation time under these conditions (~3 minutes for PBS)
- The Peress model predicted the longest evaporation time (~21 minutes)
- Which model is best under these conditions? Is a shorter or longer evaporation time more appropriate?

# Receptor fluid, Peress evaporation



# Effect of vehicle evaporation

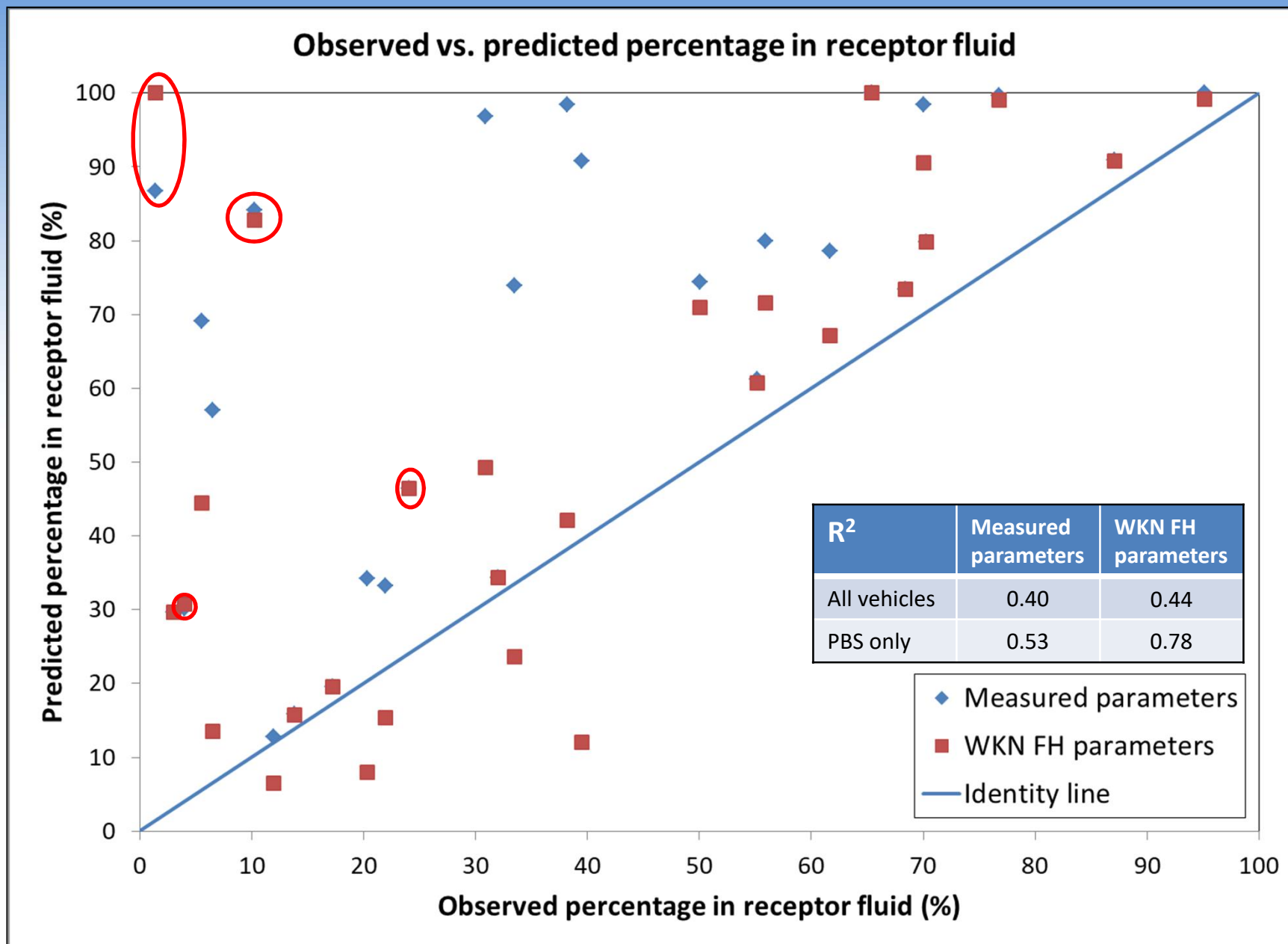
- Using the Peress equation and predicting a longer vehicle evaporation time gives similar results to the Nielsen equation
- However, the  $R^2$  is worse, so the Nielsen model is more appropriate for a default prediction under these conditions

# Effect of sebum transport

- By default, potential transport between sebum and other parts of the skin is included in the model
- However, it's unclear to what degree this transport is expected to take place under *in vitro* conditions
- There is also some question about how well our sebum permeability model can predict true sebum permeability under *in vitro* or *in vivo* conditions
- To investigate this, we modeled the compounds excluding potential sebum transport
  - Nielsen model was used for vehicle evaporation



# Receptor fluid, no sebum transport



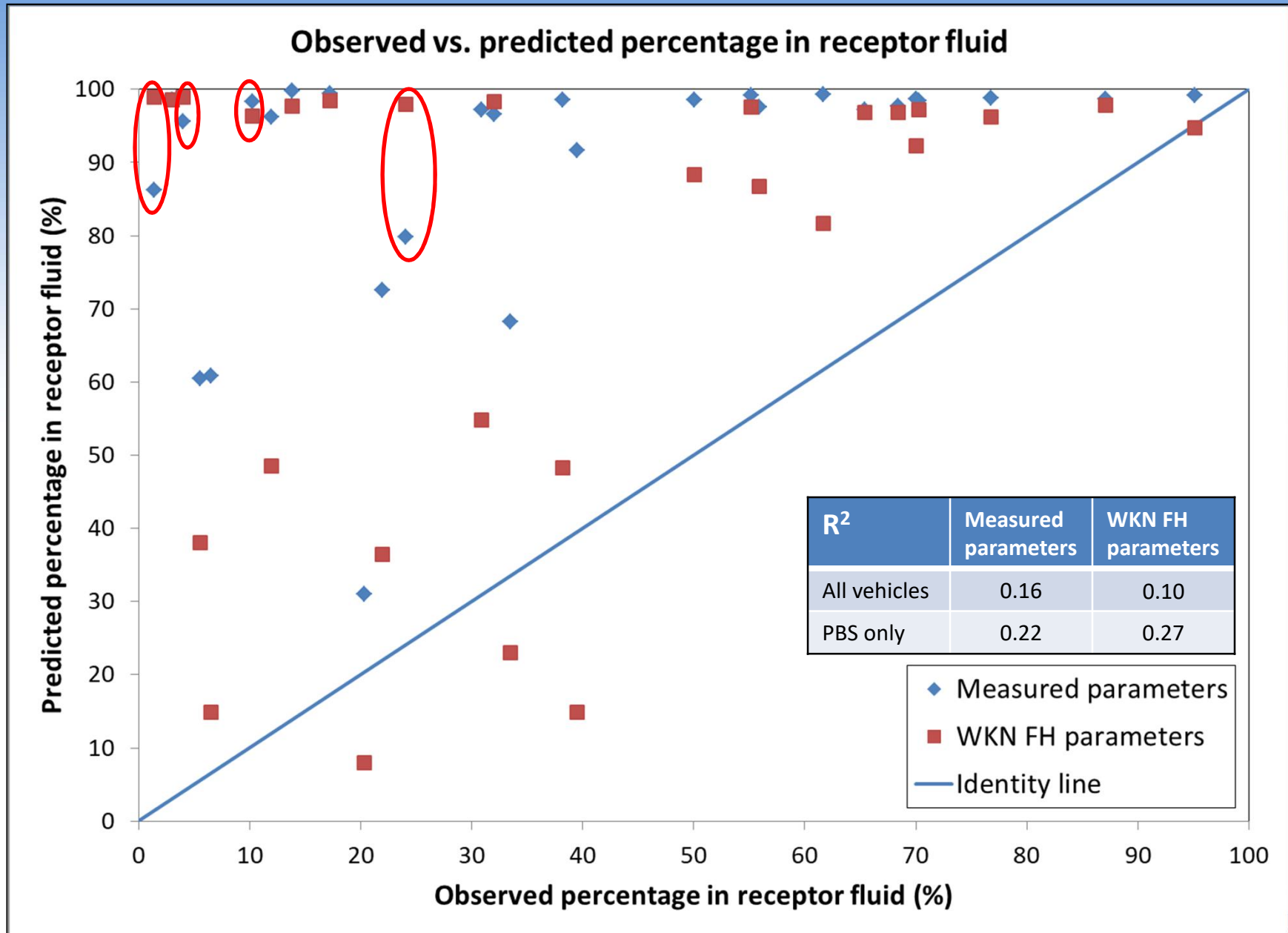
# Effect of sebum transport

- Including or excluding sebum transport had little effect on the results
- In this case, it may be because these are compounds that are of interest in cosmetics

# Compound evaporation

- In our initial predictions, we reduced the dose according to the amount of compound that evaporated (based on reported change in mass balance over 24 hours); however, we don't have an in-built mechanism to predict compound evaporation
- How accurate were our predictions without taking compound evaporation into account?

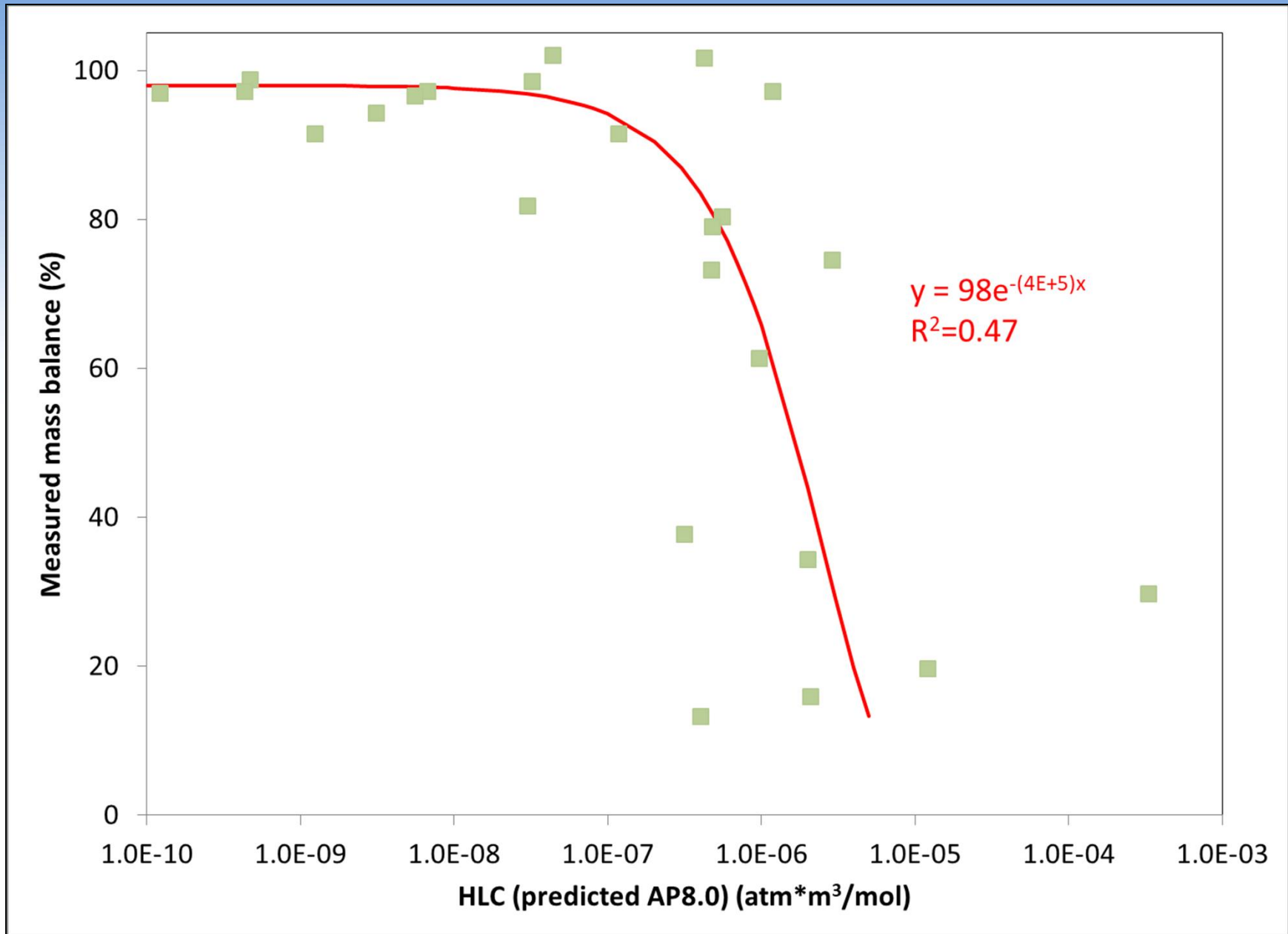
# Receptor fluid, compound evaporation not accounted for



# Henry's law constant

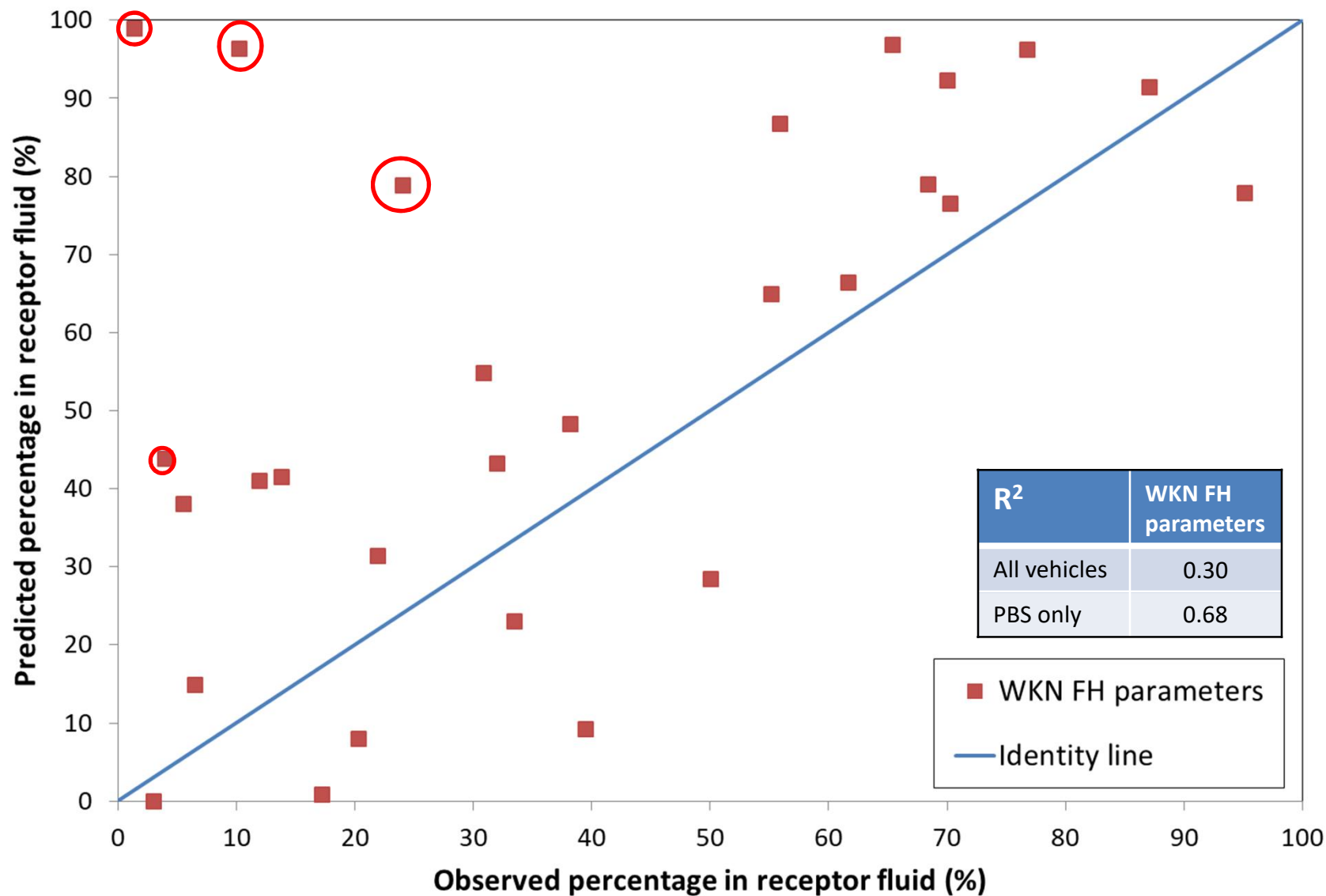
- Modeling of compound evaporation is clearly essential to predict skin permeation
- Henry's law constant can be used to determine volatility of a substance
  - This value can be predicted using ADMET Predictor™
- Can we use this property to accurately predict the volatility of a compound applied topically?
- We use only the aqueous vehicles for the fitting

# Mass balance vs. Henry's law constant



# Results using predicted compound evaporation

Observed vs. predicted percentage in receptor fluid



# Predicting compound evaporation

- Using this semi-empirical model is a great improvement on assuming no compound evaporation
- How well would this model describe compound evaporation in non-aqueous vehicles, or a different experimental protocol?
- With more data, can we build a dynamic model of how the compound might evaporate over time?

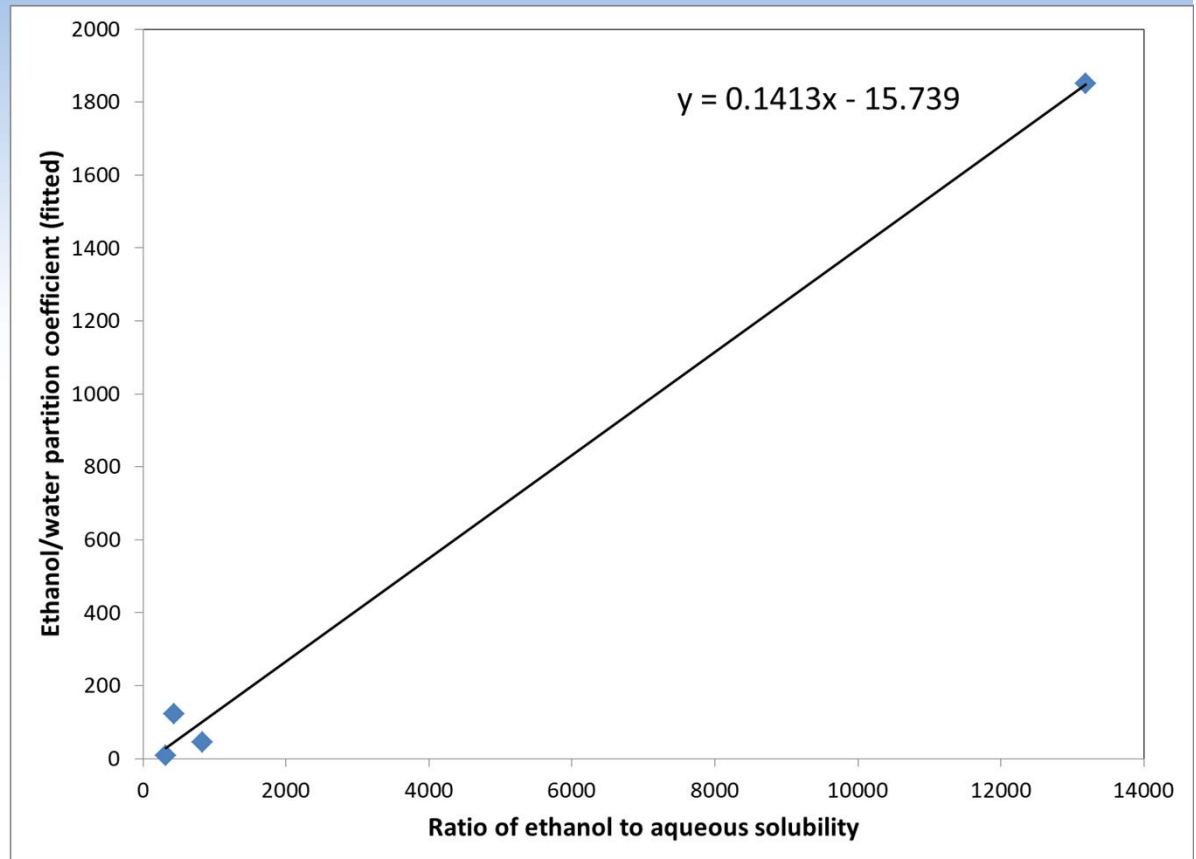


# Predicting drug delivery from ethanol vehicle

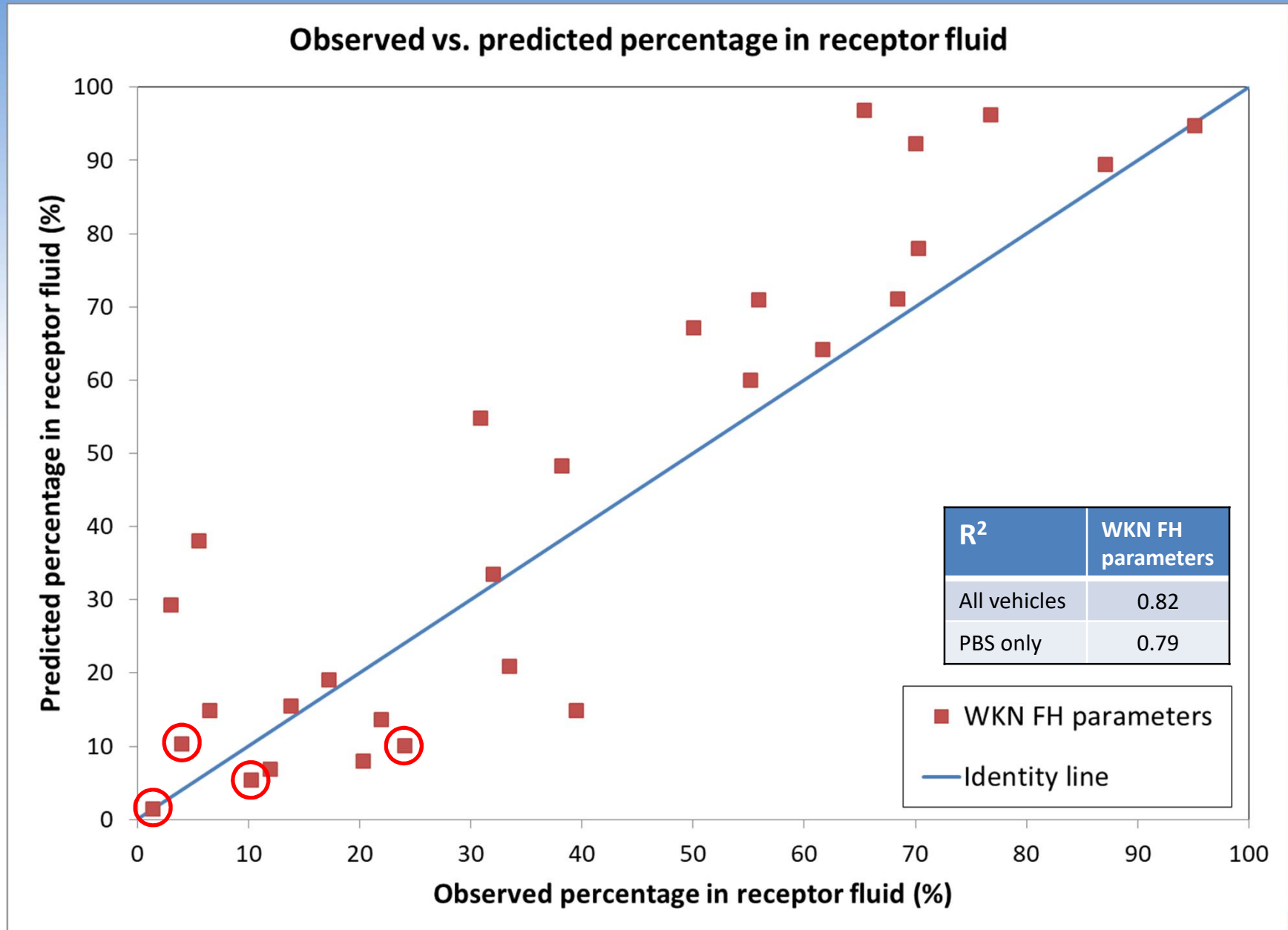
- We think ethanol vehicle is poorly modeled because partitioning into skin is significantly different between ethanol and water vehicles
- We also think this partitioning may be related to the solubility of the compound in ethanol and water
- To test this, we do a two-step process:
  - Fit an ethanol/water pseudo-partition coefficient to the amount in receptor fluid after 24 hours for each of the four compounds administered in ethanol
  - Relate this fitted value to the ratio between the ethanol and water solubilities of each compound

# Relationship between solubility and ethanol/water pseudo-partition coefficient

- We can fit a linear relationship between the solubility ratio and the ethanol/water partition coefficient
- Does using this equation improve our predictions in ethanol vehicle?



# Results using predicted ethanol/water partition coefficient



# Predicting drug delivery from ethanol vehicle

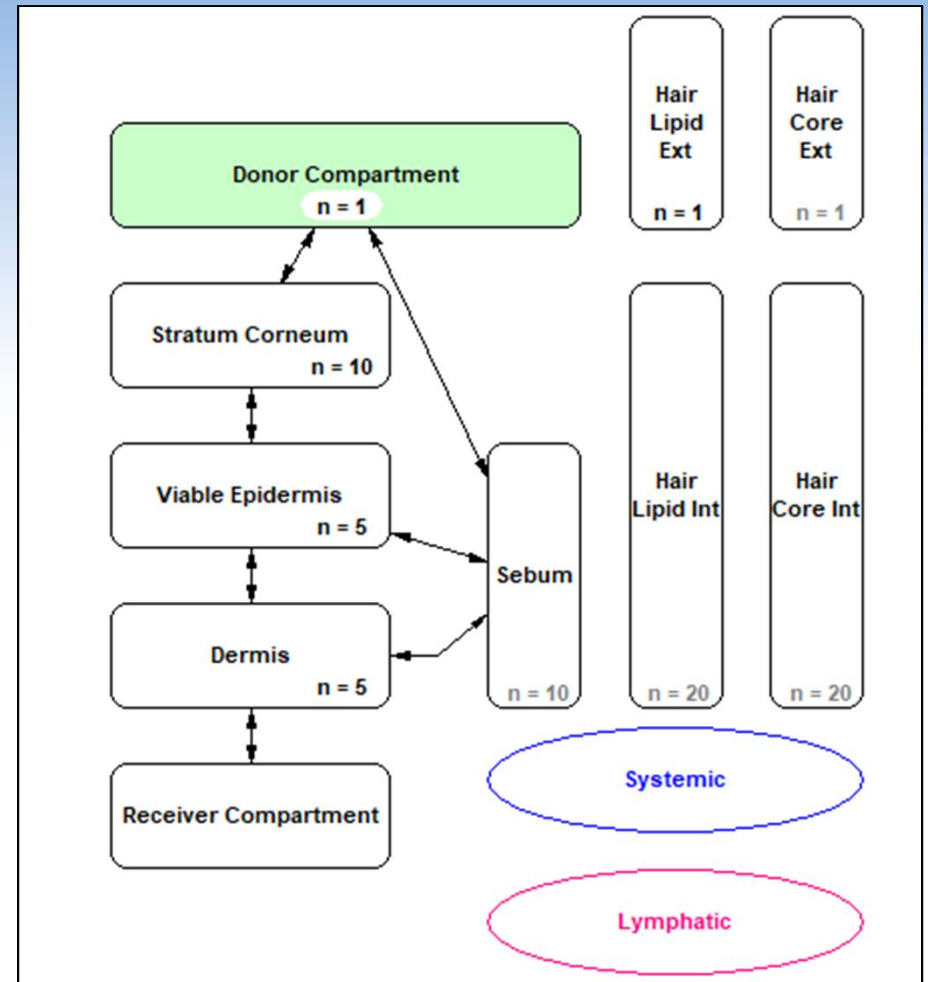
- Preliminary results suggest that there is a linear relationship between the ethanol/water solubility ratio and the ethanol/water pseudo-partition coefficient
- However, more compounds would be necessary to gain more confidence in this prediction
- Does the same relationship hold outside of this specific experimental protocol?
- Are there similar solubility relationships for other vehicles?

# Final conclusions

- Prediction of *in vitro* dermal delivery and drug in receptor fluid should be done using:
  - Nielsen model for vehicle evaporation
  - Wang-Kasting-Nitsche fully hydrated model for stratum corneum permeability
  - Kretsos model for viable epidermis and dermis permeability
- Compound evaporation should be measured or predicted according to the Henry's Law constant
- Predictions of ethanol vehicle are poor, but can be improved by scaling the vehicle/water partition coefficient according to the ratio between ethanol and water solubilities

# GastroPlus 9.6

- In GastroPlus 9.6, we have added an in vitro dermal physiology
- This is modeled as a static diffusion cell, with donor and receiver compartments



# Thank you!

- Simulations Plus
  - Viera Lukacova
  - Haiying Zhou
  - Jim Mullin
  - Robert Fraczekiewicz
- Cosmetics Europe
  - Andreas Schepky
  - Nicola Hewitt
  - Martina Klaric



# Please check out the Cosmetics Europe poster on Wednesday!

- Abstract Number/Poster Board number: 3143/P776
- Abstract Title: Cosmetics Europe Evaluation of Five *In Silico* Skin Penetration Models
- Presenting Author: Andreas Schepky
- Session Title: Alternatives to Mammalian Models III: Liver, Ocular, and Skin Alternatives
- Presentation Date: Wednesday, March 14, 2018