Cosmetics Europe evaluation of 6 *in silico* skin penetration models

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Introduction

The Cosmetics Europe (CosEu) ADME Task Force aims to evaluate and develop *in silico* skin penetration models using relevant measured values. Since there are widely differing opinions on different *in silico* models, we have evaluated 3 open source and 3 commercial models in order to identify 1-2 that will be investigated further as part of the CosEu Long Range Science Strategy. Models varied in complexity (see "Model features") but were primarily based on physical chemistry of diffusion, with different degrees of physiological relevance built in. The models were built to simulate different scenarios (e.g. *in vivo* pharmacokinetics of drugs, finite application to *in vitro* skin etc); however, we used all of them to simulate the cutaneous distribution of 25 chemicals that were run in *ex vivo* human skin penetration studies. The chemicals varied in molecular weight (110-290), LogP (-0.07-4.8), melting point (-90-104°C), boiling point (200-489°C), vapor pressure ($2.4x10^{-8}$-0.7 mmHg at 25°C) and water solubility (0.04-504 mg/l). Each partner was provided with the same set of input parameters, including physicochemical properties and details of the skin penetration protocol e.g., dose applied, application surface area, as well as the mass balance. The models were evaluated based on several aspects (see below).

Model features

Parameter	TCAT™	Simcyp	DSkin	CDC	Surrey	DermWin
Open source?	No	No	No	Yes	Yes	Yes
User-friendly interface?	Yes	Yes	Yes	Yes	No	Yes
Can CosEu K/D data be used in the current model as input?	Yes	Yes	Yes	No	Yes	No
Can the model use metabolism data?	Yes	No	No	No	Yes	No
Population/uncertainty predictions possible?	Yes	Yes	Yes	No	Yes	No

Basis of evaluation

The overall evaluation was based on several factors:

- Information gained from models e.g. impact of measured data
- Ability to predict solvent effect (PBS vs ethanol)
- Ease of use of model and training required
- Required input parameters and consideration of parameters that may influence prediction
- Advantages and disadvantages of models e.g. regulatory acceptance, open source etc
- Statistical analysis – there is a limited use of a model that cannot approximate dermal delivery (DD)

Statistical analysis of dermal delivery

Statistical analysis of the predicted vs measured dermal delivery of 24 chemicals applied in PBS

Each chemical is denoted with a number, blue line = linear regression line; dotted red line = LOESS (non-linear relationship observed); grey line = line of unity.

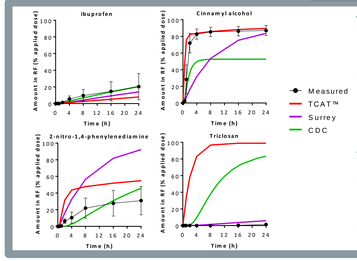
DermWin not evaluated

Parameter	TCAT™	Simcyp	DSkin	CDC	Surrey
DD – Slope (blue line)	0.80	0.66	0.57	0.70	0.44
DD - Residual standard error (RSE)	12.1	19.0	17.4	17.9	23.7
DD - R^2	0.80	0.52	0.60	0.58	0.25
No. under-predicted by >1.5fold	1	1	4	10	0
No. over-predicted by >1.5fold	4	7	6	1	8

Different input parameters were used by different partners, from 1 (SMILES for DermWin) to 16. In addition, TCAT™, Simcyp and Surrey simulations incorporated the mass balance as a measure of chemical volatility.

The prediction of the DD of 24 chemicals applied in PBS varied between the models (one chemical was applied in ethanol). The best correlation was observed for the TCAT™ model, with only 2 outlier chemicals over- or under-predicted. While the R^2 of for the Surrey model was low, this was mainly due to a cluster of chemicals that were markedly over-predicted. The over-prediction of DD by 3 models is considered to be conservative in terms of human safety assessment. The predicted values were general well predicted, with RSE values being within 12% to 24% of the observed mean value of DD (blue line).

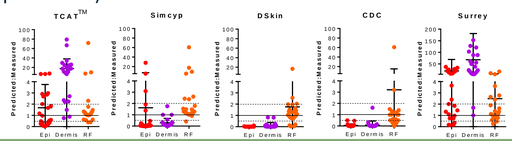
Prediction of receptor fluid kinetics



Three models were used to predict the receptor fluid (RF) kinetics. Some kinetic profiles were well predicted by all 3 models (e.g. ibuprofen) and others were better predicted by one or the other model (see examples). The kinetics of 12, 7 and 9 chemicals were well predicted by the TCAT™, Surrey and CDC models, respectively (the predicted amounts in the RF was similar to measured values at all time points); while 8, 11 and 9 of the chemicals were predicted relatively well (e.g. cumulative amount was similar after 24 h but the overall kinetics profile differed). The kinetics of 5, 7 and 7 chemicals were poorly predicted by the TCAT™, Surrey and CDC models, respectively.

Prediction of amounts in skin compartments

The ability to predict the amounts in epidermis (Epi) and dermis varied between models; however, the maximum amounts measured in *ex vivo human* skin were only 10% and 3% of the applied dose, respectively. The predicted amounts in the receptor fluid (RF) by each model were generally within 2-fold of the measured values (which ranged up to 95% of the applied dose).



Evaporation and solvent effects

None of the models adequately predicted the amount of chemical that evaporated. This was shown to be important since the prediction of dermal delivery (DD) was improved when the evaporated amount was accounted for in the simulations (estimated using the mass balance) (data not shown).

The measured DD of 3 chemicals using *ex vivo* human skin was lower when they were applied in ethanol compared to PBS. This effect was predicted well by the CDC model and was generally indicated by the other 4 *in silico* models, although they over-predicted the DD after application in ethanol (data not shown).

Conclusion

- In conclusion, our evaluation highlighted important differences in the models.
- The EPA DermWin model was included because it is used by safety assessors; however, it predicts Kp and is not suitable for the prediction of DD or cutaneous distribution and was therefore excluded from several comparisons.
- The 5 more complex *in silico* models could predict the DD of chemicals relatively well, especially if the fraction evaporated was considered.
- Amounts of chemical in the epidermis and dermis were less well predicted, as was the amount evaporated. However, there was a good prediction of RF kinetics by the 3 models in which these simulations were run.
- Future work will investigate how measured data can be used to improve the models further.

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