The Cosmetics Europe (CosEx) ADMTE Task Force aims to evaluate and develop in silico skin penetration models using relevant measured values. Since there are widely differing opinions on different 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 CosEx Long Range Strategy. Models varied in complexity (see “Models features”) but were primarily based on chemical physics 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 (-0.7-4.8), melting point (90-104°C), boiling point (100-489°C), vapor pressure (2.4×10^-7 mbar 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).

**Statistical analysis of dermal delivery**

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 R² of 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 generally 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 (ibuprofen) and others were better predicted by one or the other model (e.g. ketoprofen). 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 kinetic profile differed). The kinetics of 5, 7 and 6 chemicals were poorly predicted by the TCAT™, Surrey and CDC models, respectively.

**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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- T. Chen (University of Surrey) (conducted “Surrey” simulations)
- Scientific Compliance (conducted Dermskin simulations)

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**Introduction**

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)

**Basis of evaluation**

- Open source?
- User-friendly interface?
- Is the input data in the current model as input?
- Can the models use metabolised data?
- Is the measured data sufficient to evaluate the model predictions? (yes/no)

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

The ability to predict the amounts in epidermis (Epo) 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).

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