



Epidermal disposition kinetics of sensitising chemicals

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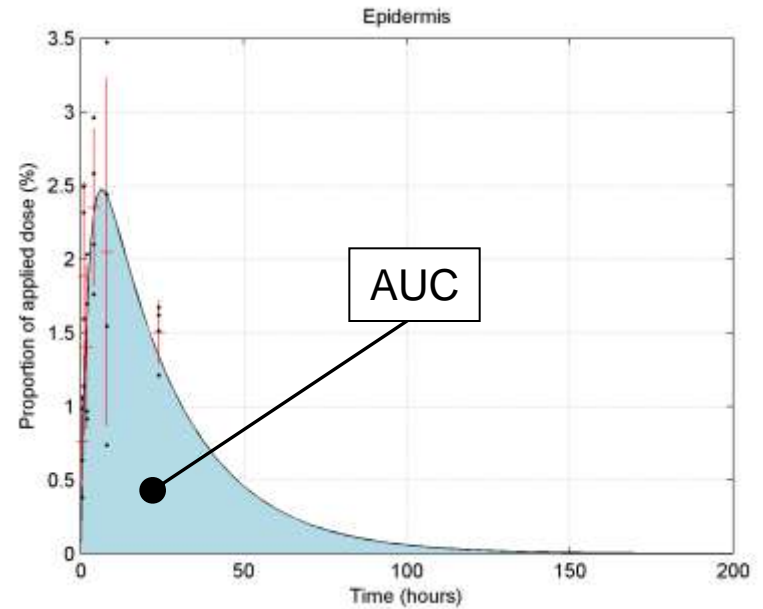
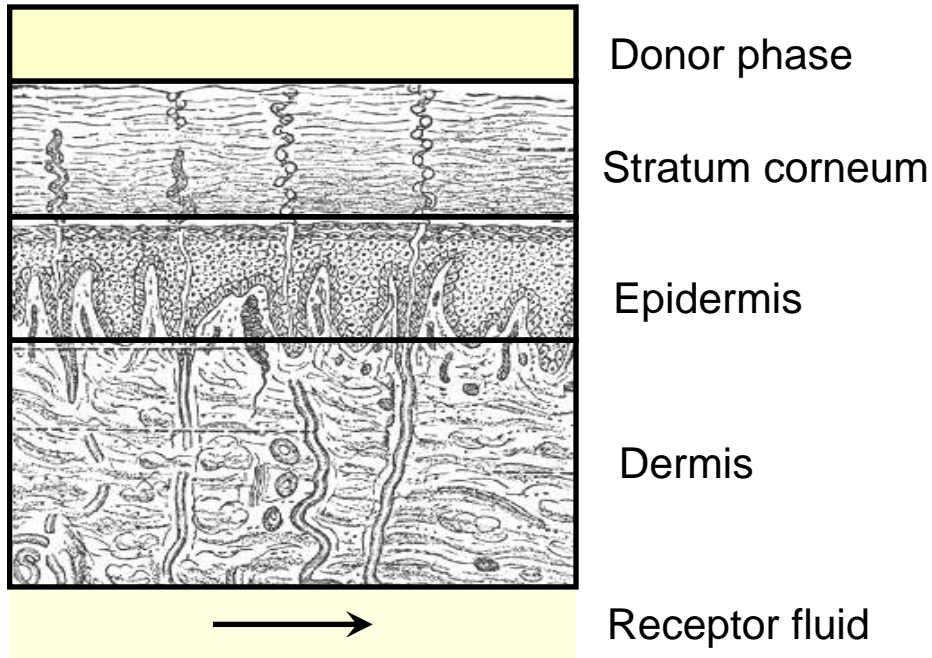
Safety and Environmental Assurance Centre



Skin sensitisation and risk assessment

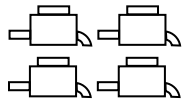
- Key occupational and consumer safety endpoint
- Can lead to the disease state allergic contact dermatitis
- Animal tests are currently used to help assess sensitisation **hazard**
- Unilever has an ongoing research programme to develop novel ways of assuring consumer safety without animal testing
- Sensitisation **risk** is a function of both **hazard** and **exposure**
- Improving our understanding of exposure can help assure safety by:
 - Understanding how exposure affects risk of sensitisation
 - Refining our exposure measurements
 - e.g. in the epidermis - resident site of mediating cells

Pharmacokinetic motivation

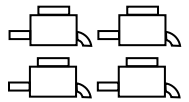


- AUC summarises information about concentration and time
- Use compartmental model to calculate epidermal AUC from data

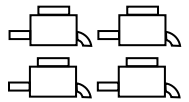
Time-course skin permeation assay



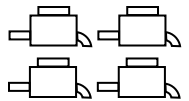
■ 1/2 hour



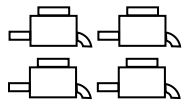
■ 1 hour



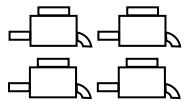
■ 2 hours



■ 4 hours



■ 8 hours



■ 24 hours

n = 3 or 4 cells

Hourly collection of receptor fluid

Pendlington *et al*
Cutaneous and Ocular Toxicology
27:4, 283-294, 2008

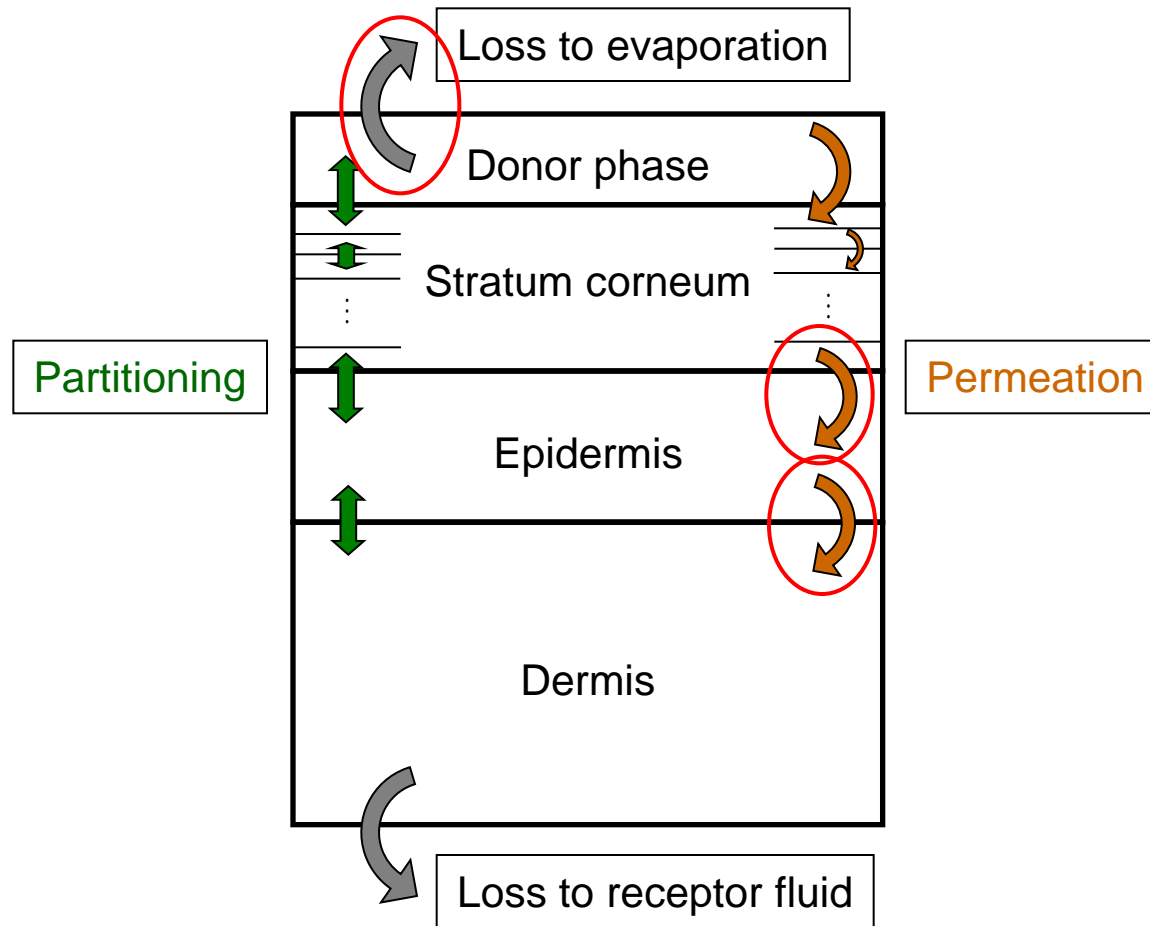
Sampled:

- Donor phase
- Stratum corneum
- Epidermis
- Dermis

Chemicals tested

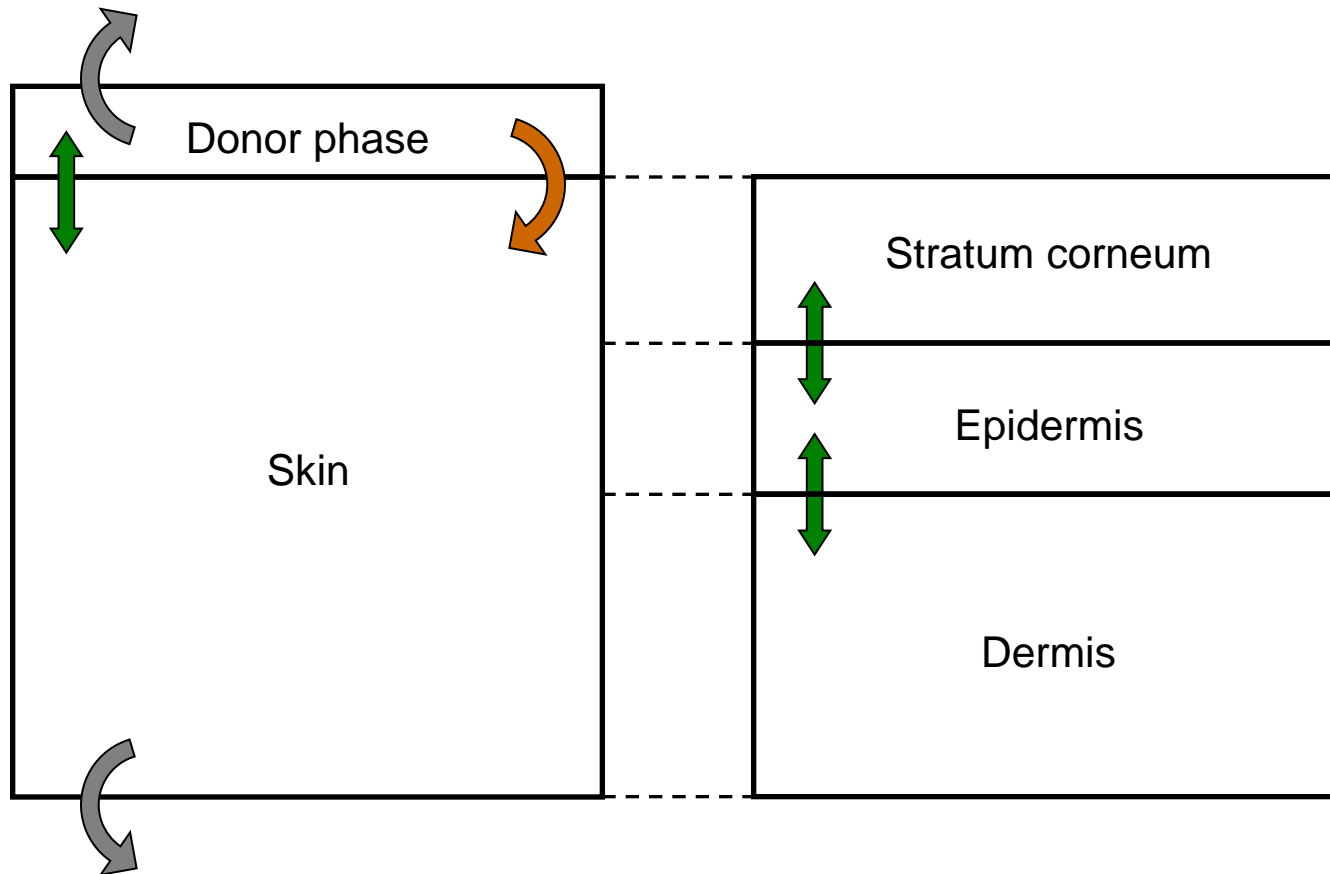
- Pendlington *et al*: cinnamic aldehyde in four different vehicles
 - propylene glycol
 - acetone-olive oil (4:1 v/v, AOO)
 - ethanol
 - aqueous ethanol (1:1 v/v)
- Subsequently: 12 further chemicals in AOO
 - 10 sensitisers and 2 non-sensitiser
 - log P from 0.6 to 9.0
 - Tested by Charles River or Unilever SEAC

Full skin layer model



- 10 parameters in total
- Investigated parameter variability (on average across all chemicals)

Combined skin layer model



- Much simpler basic model with 4 parameters

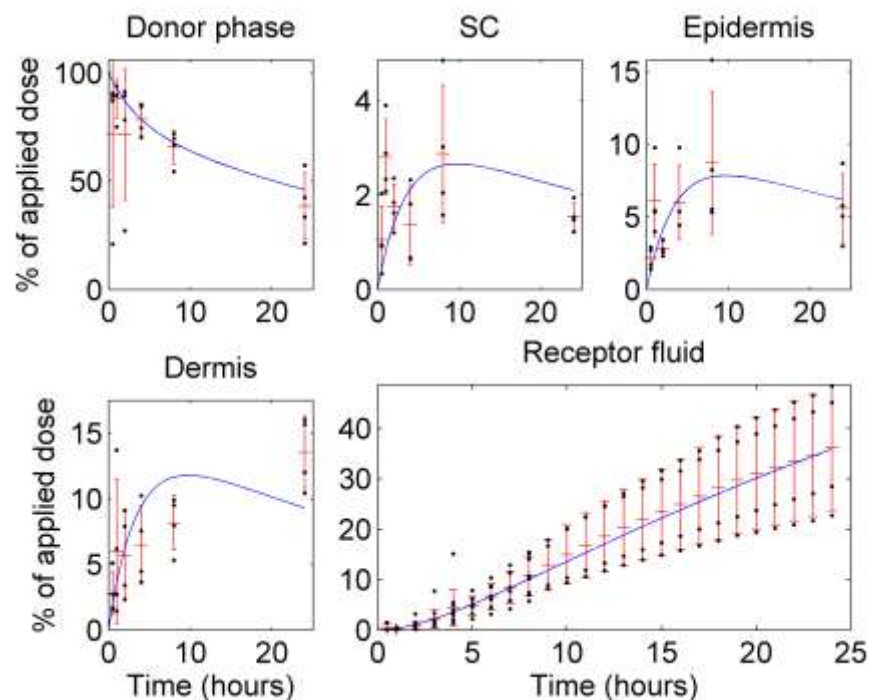
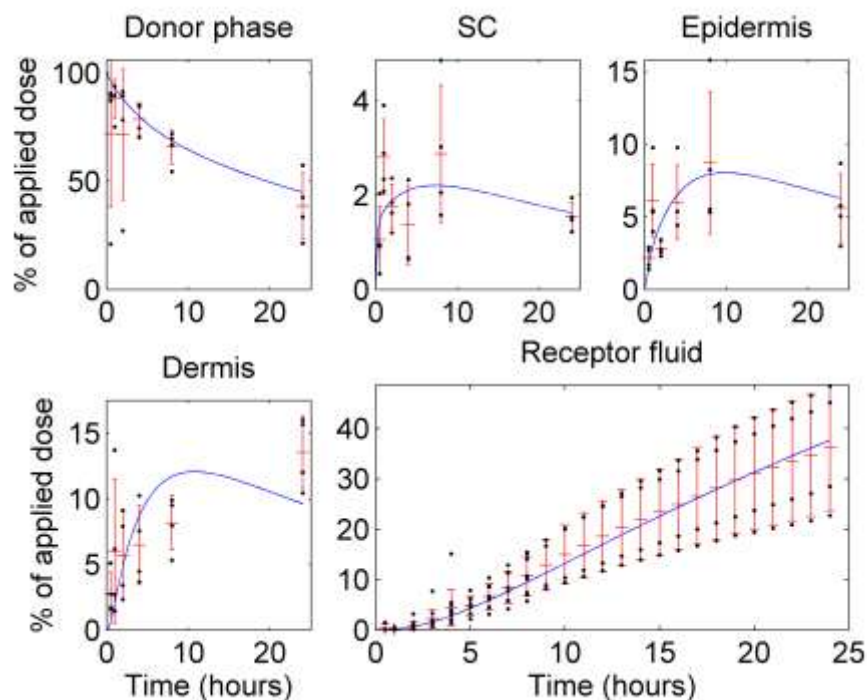
Model comparison: Moderately hydrophobic chemical

Full skin layer model

AUC/dose = 11.7 hrs

Combined skin layer model

AUC/dose = 12.2 hrs



- 1,4-dihydroquinone (log P = 0.6) 75mM in AOO

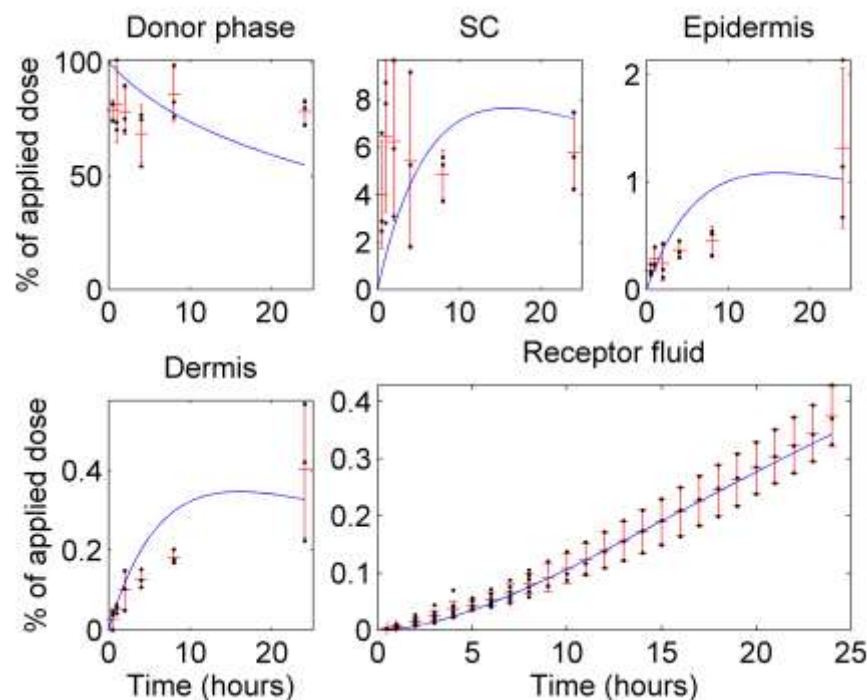
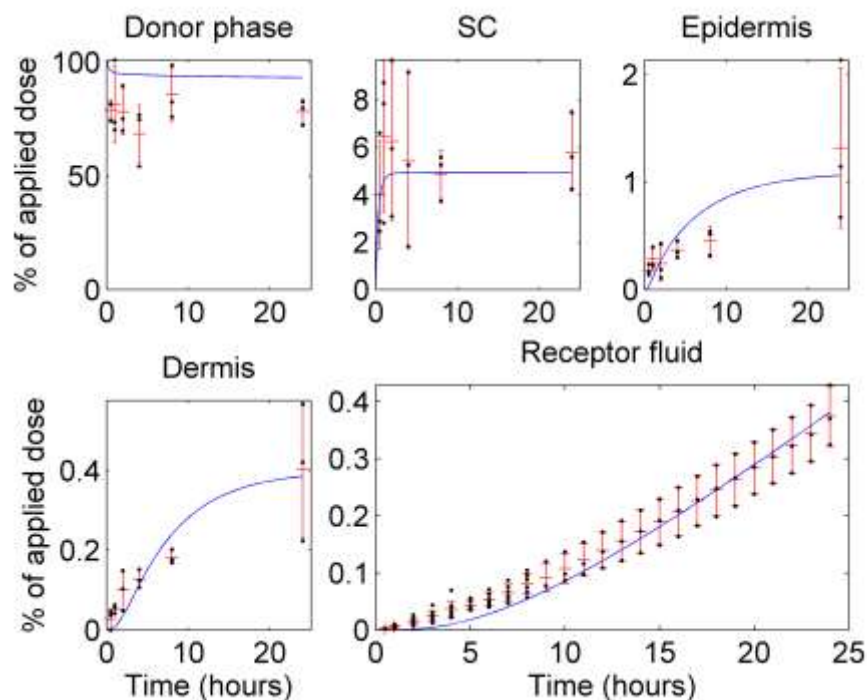
Model comparison: Extremely hydrophobic chemical

Full skin layer model

AUC/dose = 14.9 hrs

Combined skin layer model

AUC/dose = 2.3 hrs



- α -hexyl cinnamic aldehyde ($\log P = 5$) 189mM in AOO

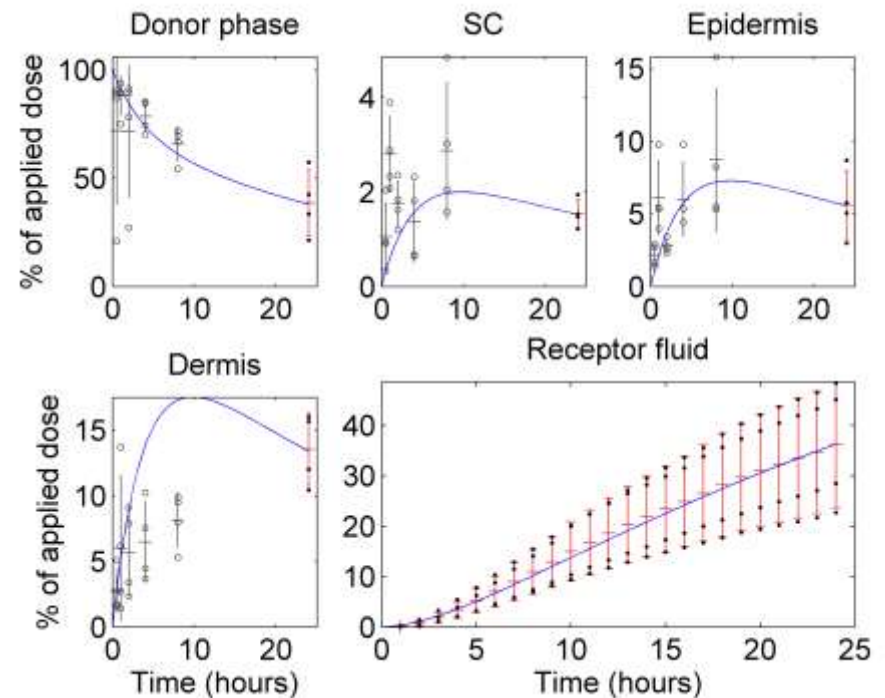
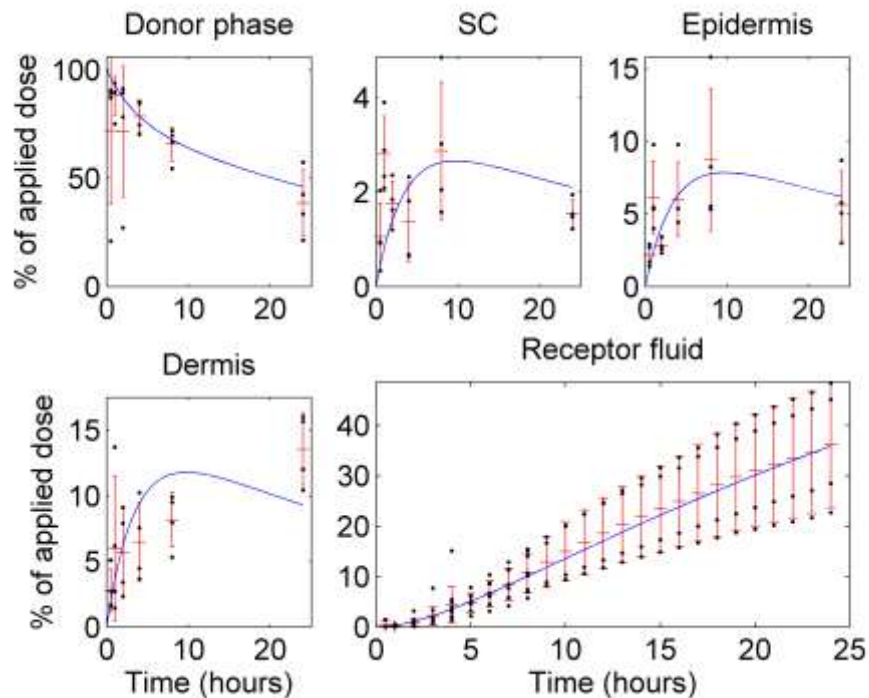
Use of 24 hour samples only

All data

AUC/dose = 12.2 hrs

24 hour samples only

AUC/dose = 10.0 hrs



- 1,4-dihydroquinone (log P = 0.6) 75mM in AOO

Conclusions

- Generated time-course skin permeation data for 13 chemicals in total
- Determined AUC as parameter of epidermal disposition kinetics and potential exposure measurement for sensitisation risk assessment
- Considered full and combined skin layer models
 - Combined skin layer model has advantages of simplicity and computational speed
 - More detailed description in full skin layer model provides greater accuracy for extremely hydrophobic chemicals
- AUC can be calculated from 24 hour sampled data only, for moderately hydrophobic chemicals
- Substantial consistent set of kinetic skin permeation data, of use in development of predictive *in silico* models, e.g.
 - Kasting *et al*, 2008, J Occ Environ Hygiene 5 633
 - Chen *et al*, 2008, Ind Eng Chem Res 47 6465



Acknowledgements

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