Skin Absorption of (volatile) Liquids: A skin-PBPK Model

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Starting points of SkinPerm

A guesstimate of systemic absorption from dermal exposure to substances by using simple retrievable information:

- molecular weight
- water solubility (mg/litre)
- vapour pressure (Pascal)
- log(octanol/water) at pH 5.5 (skin pH)
- density (mg/cm3)

Estimate 1st step:

- Aqueous skin permeation coefficient Kaq (QSAR) from Log(Kow), Mw (ten Berge 2009)
- Skin/water partition coefficients Psw (QSAR) from Log(Kow), (ten Berge 2009)
- Skin permeation coefficient neat substance Kaq/Psw
- Maximum available volume for absorption in SC is 0.4 ml
- Estimate maximum mass in SC in equilibrium with a saturated aqueous solution (= Maq)
- Actual mass in stratum corneum is Msc
- Postulate that,
  ⇒the systemic absorption rate is related to Msc/Maq
  ⇒the systemic absorption rate is maximum at Msc ≥ Maq

Estimate 2nd step:

- Evaporation from liquid substance layer on the skin according to REACH Guidance App R14.1
- Evaporation rate from stratum corneum using the Henry coefficient and aqueous permeation coefficient Kaq
- Postulate that:
  ⇒the evaporation rate is related to Msc/Maq
  ⇒the evaporation rate is maximum at Msc ≥ Maq

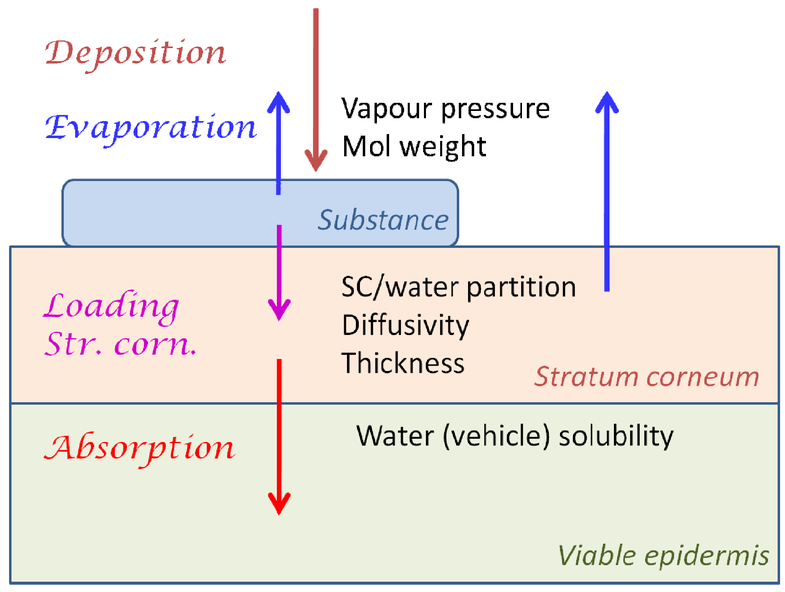
Output:

Parameters as function of the time after the start of exposure:

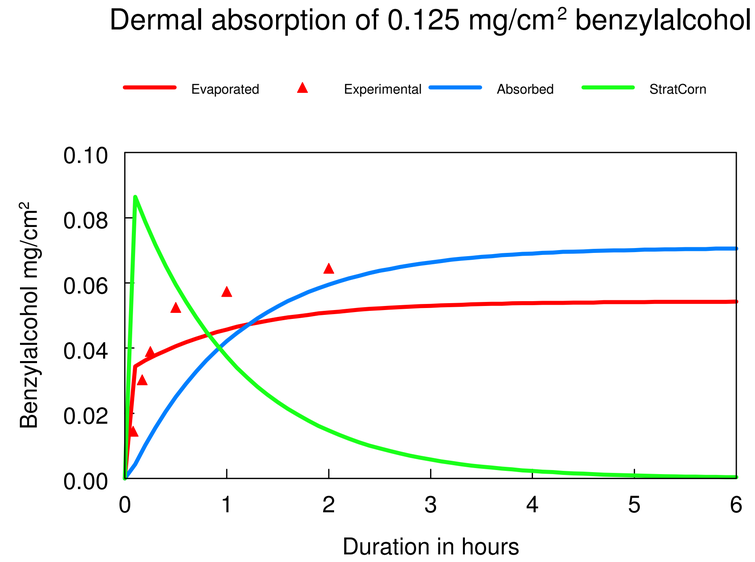
- the mass of the substance upon the skin
- the mass of the substance in the stratum corneum
- the mass of the substance evaporated
- the mass of the substance absorbed

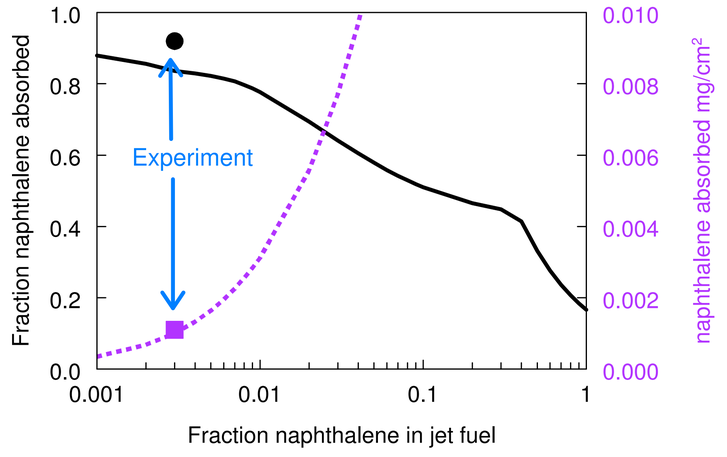
Conclusions:

- Simulation of evaporation from, metabolism in and permeation through the skin was done on the basis of QSARs and physical behaviour
- Simulations were in line with experimentally observed evaporation and absorption for a number of studies (see references)
- This method is to be used for risk assessment of dermal absorption of industrial chemicals (REACH)
- This method might be helpful to improve the design of experimental dermal absorption studies



Comparison of observed and estimated absorption of volatiles		
Substance	Absorption Observ. %	Absorption Estim. %
Benzene	0.2	0.4
Benzylalcohol	48.0	57.0
Linalool	42.5	22.9
Dihydromyrcenol	34.2	38.9
10-Undecanal	54.7	47.5
Citronellol	58.8	57.3
2-Phenylethanol	83.4	56.0
(E)-Cinnamic alcohol	96.3	59.1
Alpha-Damascone	43.0	45.5
Cis-7-p-Menthanol	53.1	66.4
2,2,2-Trichlorophenyl-ethylacetate	59.5	50.7
MPCC	76.3	84.4
(E)-2-Benzylidene-Octanal	95.7	88.8
15-Pentadecanolide	93.4	96.2





Application of 7.8 mg/cm² fluroxypyrmeptyl on human skin (hydrolysis rate 0.01/hr) Result after 48 hours		
Type of sample	% radiolable measured	% radiolable estimated
Receptor fluid	0.438	0.274
Skin residue	2.3	7.31
Mass on skin	97.3	92.4

References

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