A skin PBPK-model

Evaporation and absorption

CEFIC-LRI project

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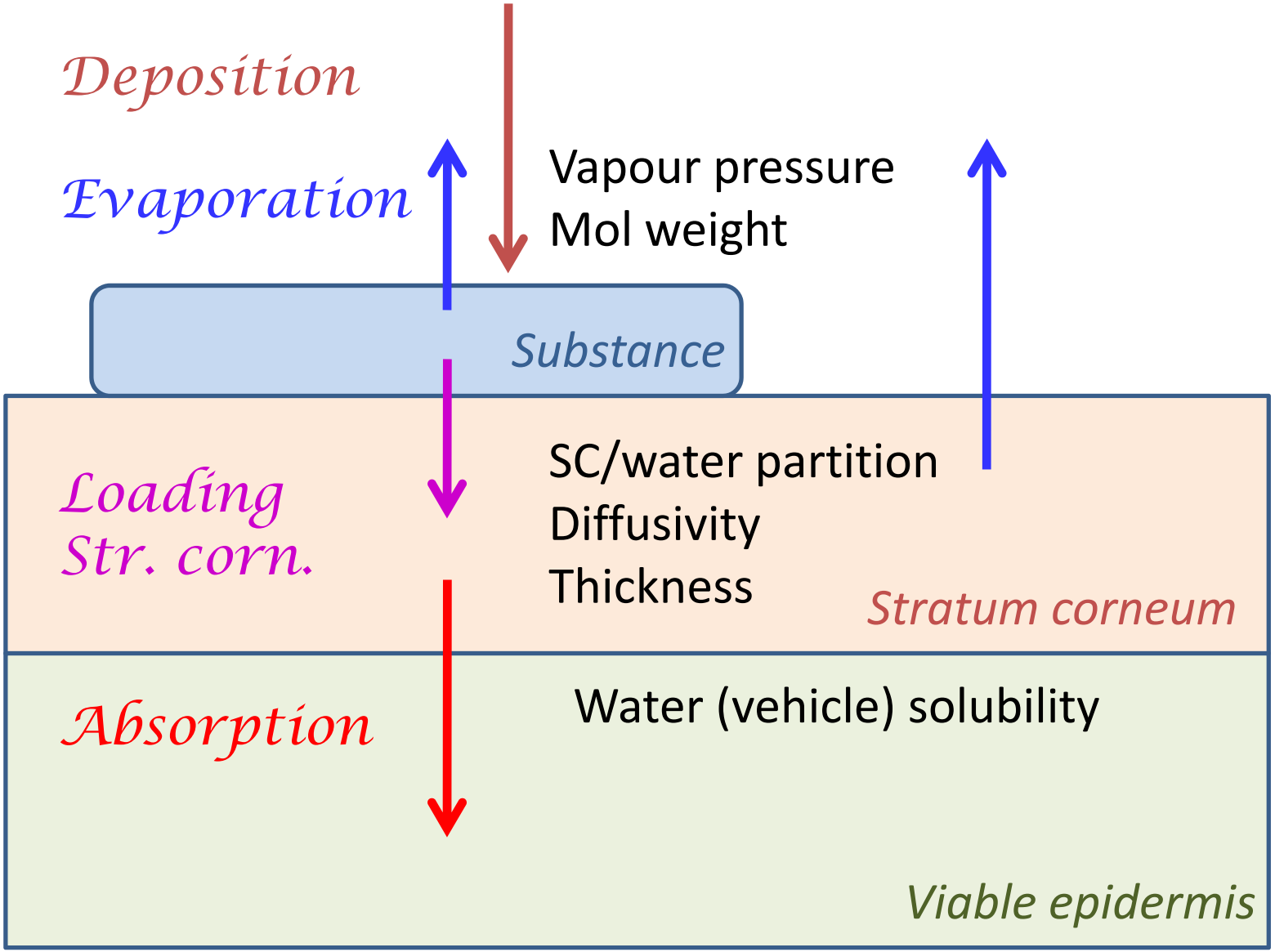
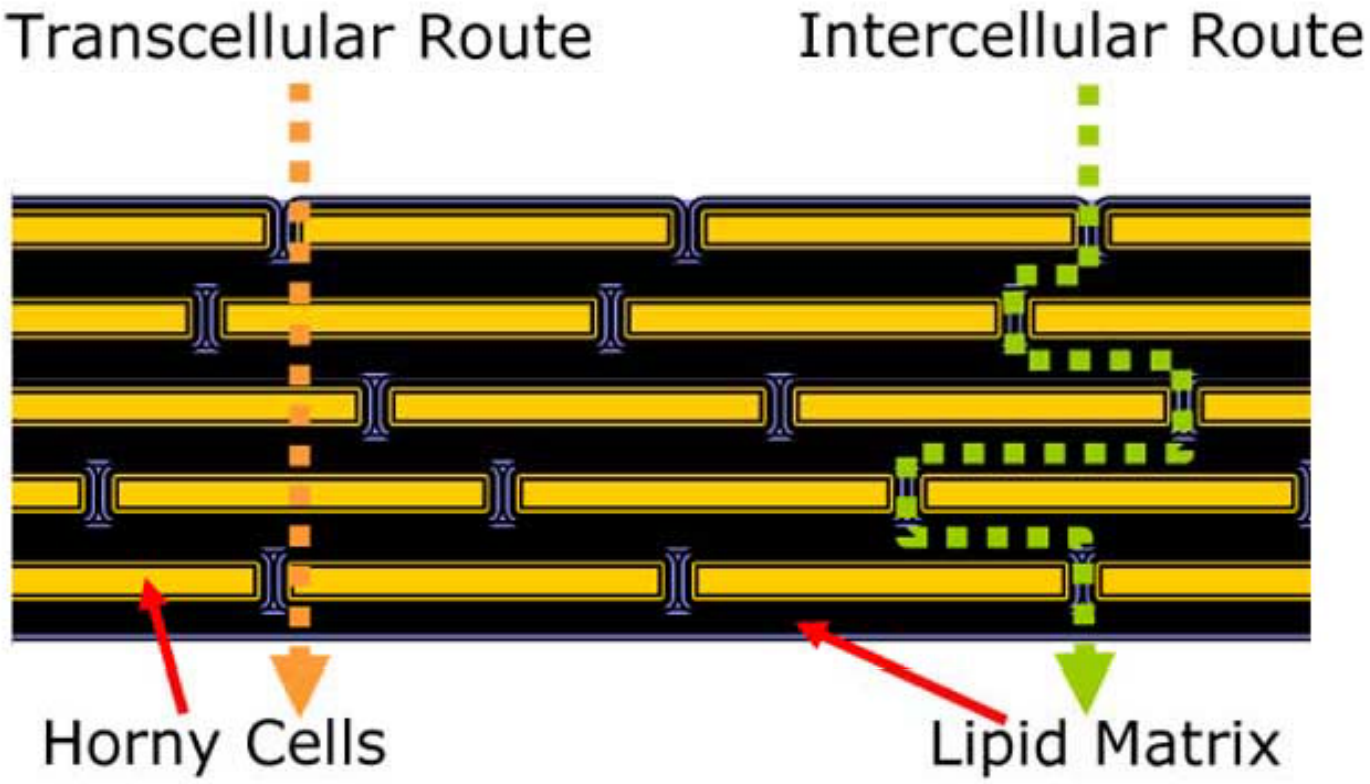
Starting points of SkinPerm(1)

- 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)


Deposition
Evaporation
Vapour pressure
Mol weight
Substance
Loading
Str. corn.
SC/water partition
Diffusivity
Thickness
Stratum corneum
Absorption
Water (vehicle) solubility
Viable epidermis

Dermal permeation process
(Cognis Skin Care Forum)



Starting points of SkinPerm(2)

- by using simple assumptions:
  - Kaq = Aqueous skin permeation coefficient (QSAR)
    - Log(Kow), Mw (ten Berge 2009)
  - Psw = Skin/water partition coefficients (QSAR)
    - Log(Kow) (minimum -1.38) (ten Berge 2009)
  - Skin permeation coefficient neat substance
    = Kaq/Psw
  - Maximum absorption in SC is 0.4 ml

Starting points of SkinPerm(3)

- by using simple assumptions:
  - estimate maximum mass in SC in equilibrium with a saturated aqueous solution (= Maq)
  - Msc is the actual mass in stratum corneum
  - postulate that,
    - the systemic absorp. rate is related to Msc/Maq
    - the systemic absorp. rate is maximum at Msc ≥ Maq

Starting points of SkinPerm(4)

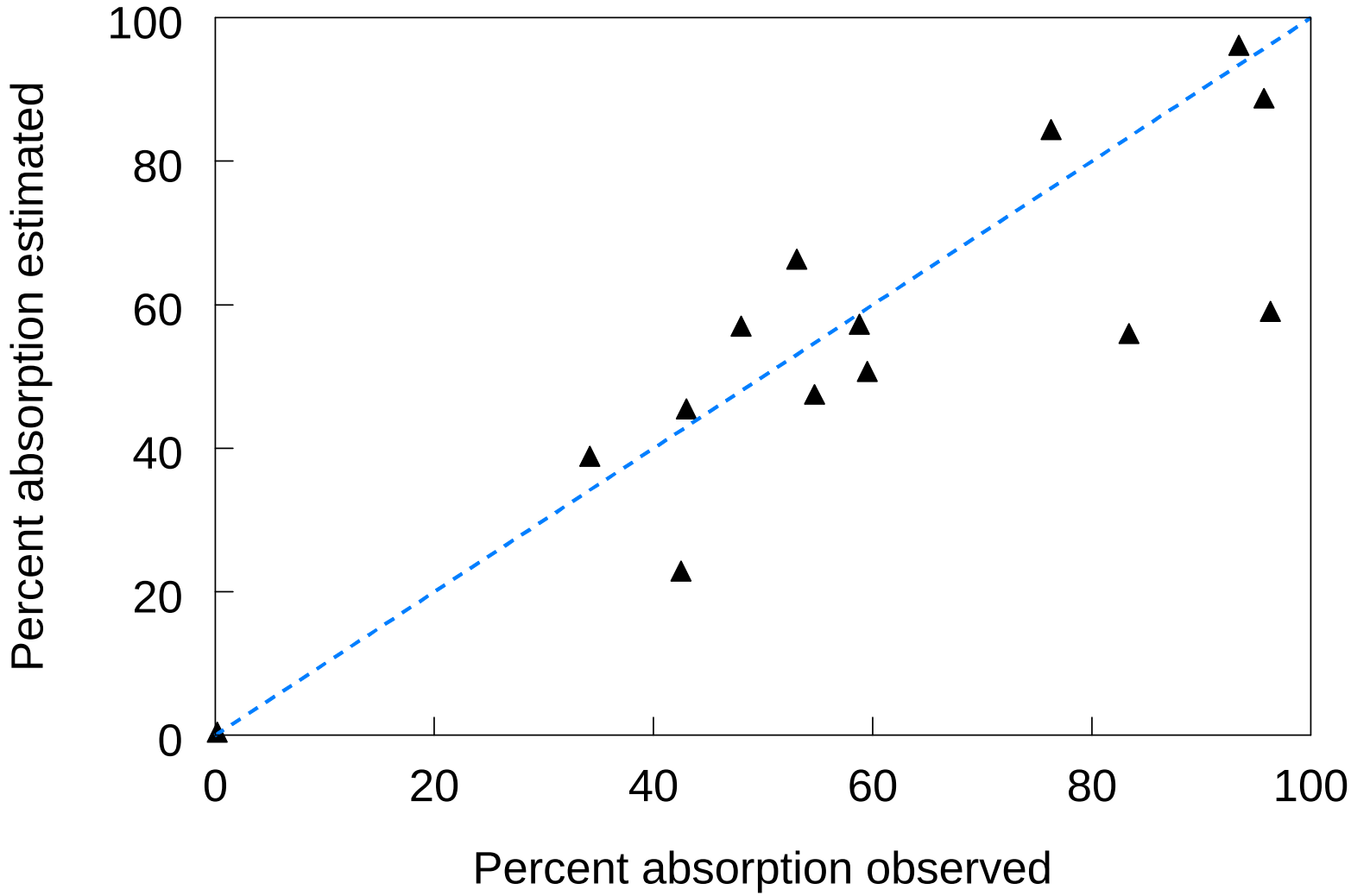
- by using simple assumptions:
  - estimate evaporation from substance layer on the skin according to REACH Guidance App R14.1
  - evaporation rate from stratum corneum related to Henry coefficient and aqueous perm.coeff. Kaq
    - the evaporation rate is related to Msc/Maq
    - the evaporation rate is maximum at Msc ≥ Maq

Evaporation of non-occluded skin doses

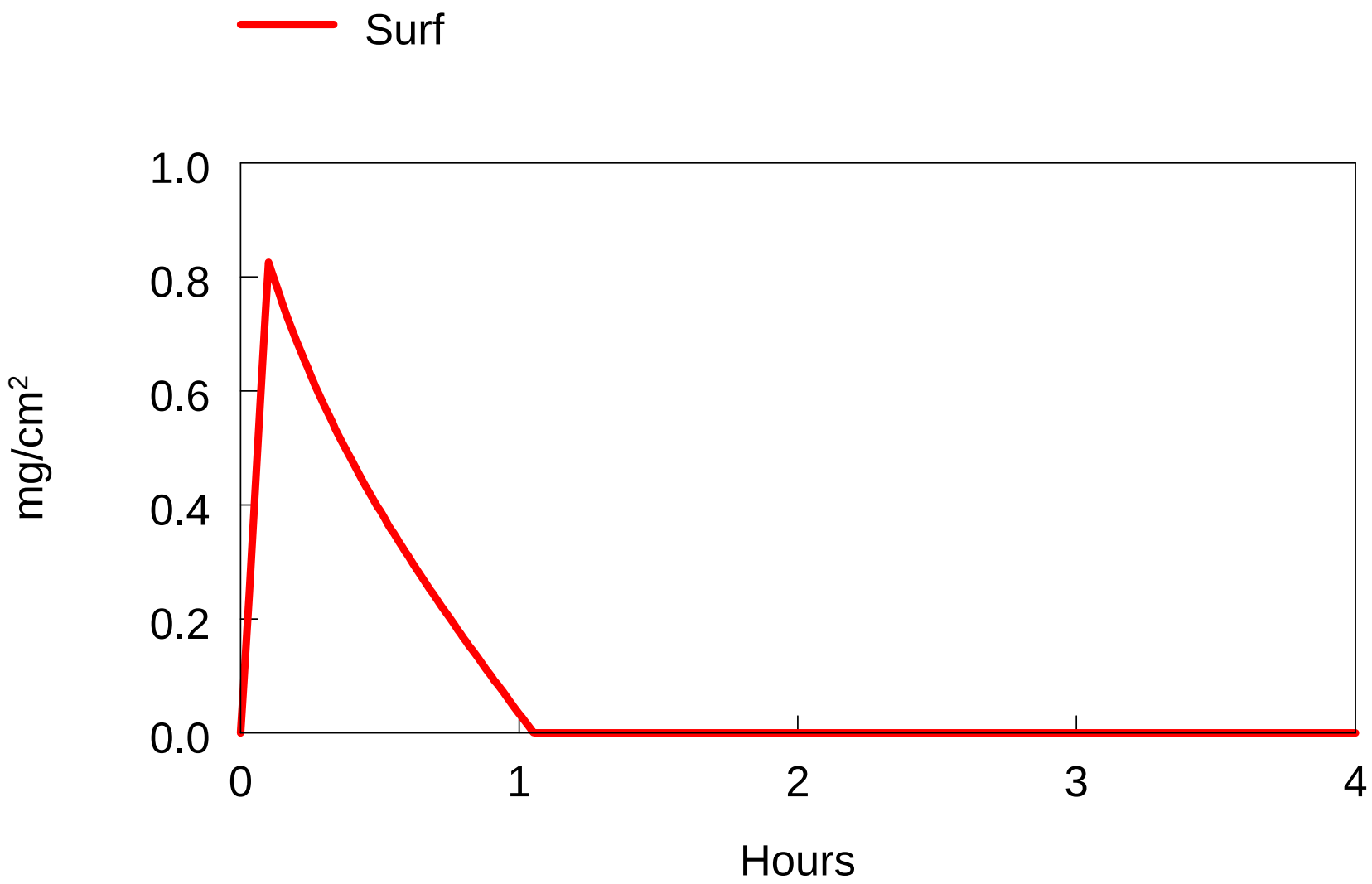
- Modjtahedi & Maibach (2008) Benzeen
- Sayasombati & Kasting (2004) Benzylalcohol
- Vuilleumier, Flament & Sauvegrain (1995)
  12 perfume ingredients in alcohol
- Kasting & Saiyasombati (2001)
  Evaluation Vuilleumier et al. (1995)

Substance Absorption	% observed	% estimated
Benzene	0.2	0.4
Benzyl alcohol	48	57
Linalool	42	23
Dihydromyrcenol	34	39
10-Undecanal	55	48
Citronellol	59	57
2-Phenylethanol	83	56
(E)-Cinnamic alcohol	96	59
α-Damascone	43	46
Cis-7-p-Menthanol	53	66
2,2,2-Tri-chlorophenylethylacetate	59	51
MPCC	76	84
(E)-2-Benzylidene Octanal	96	89
15-Pentadecanolide	93	96

Absorption volatiles % Observed / Estimated



Deposition of benzylalcohol (1mg/cm^2 in 6 min)



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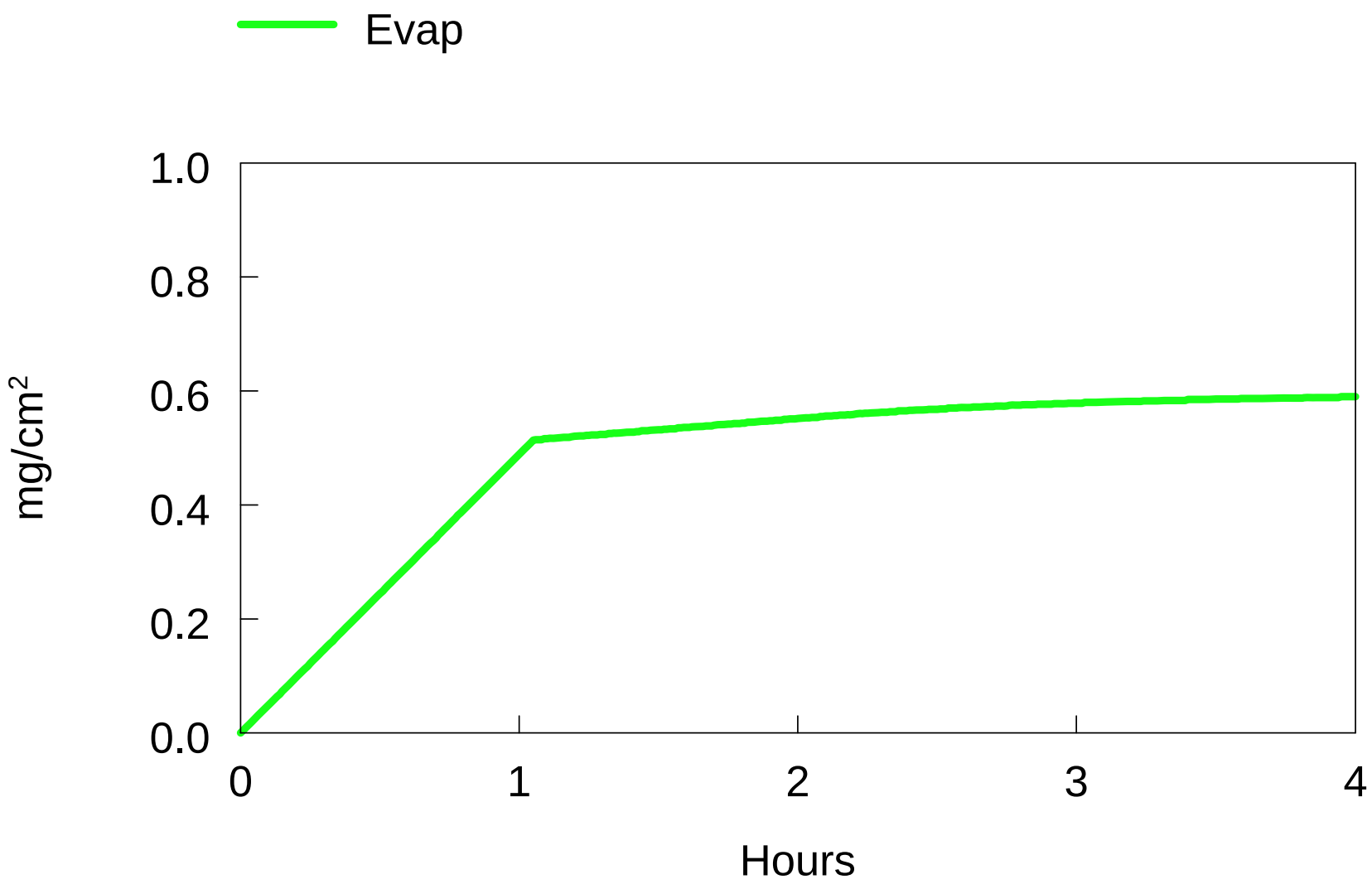

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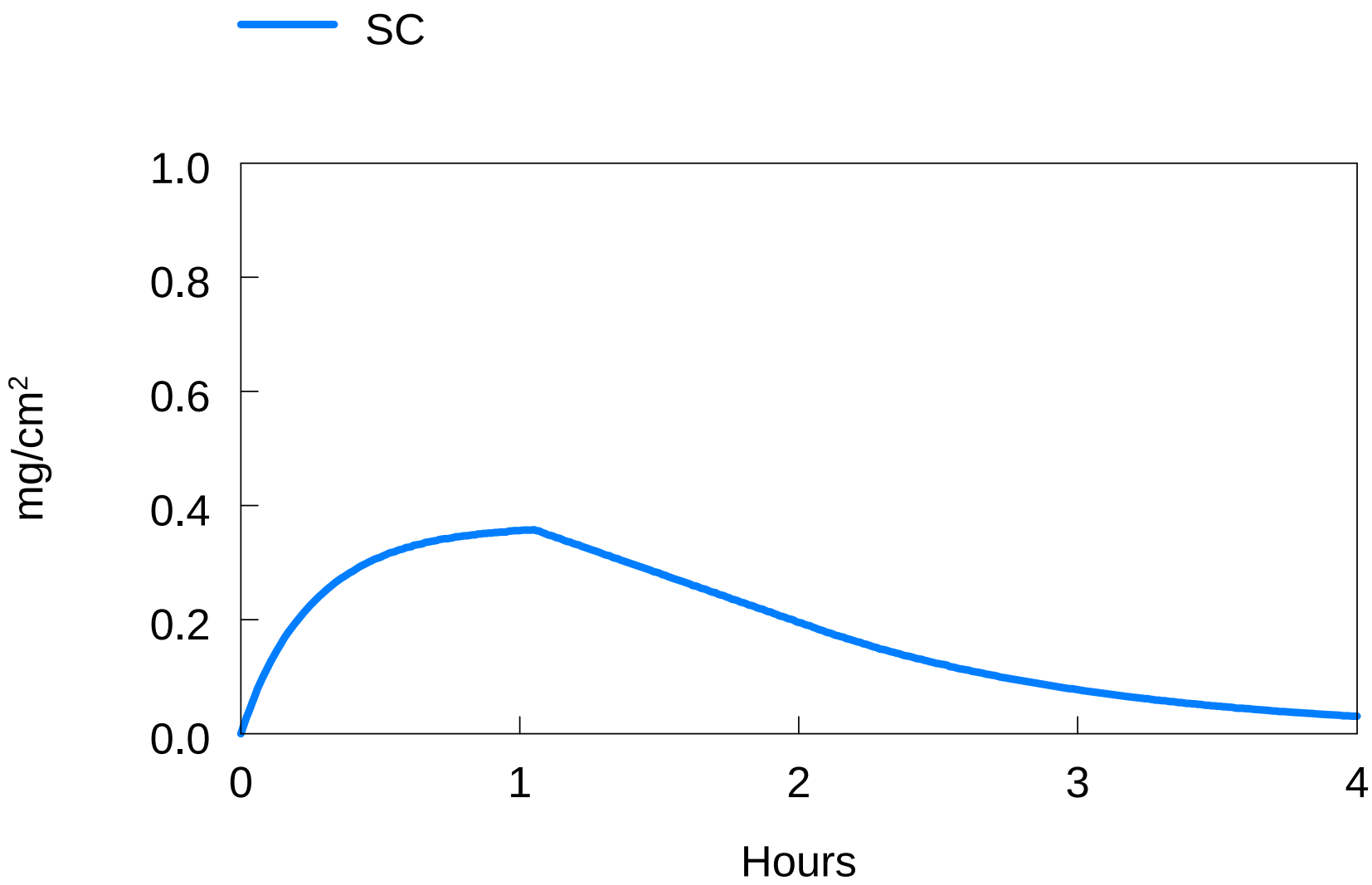
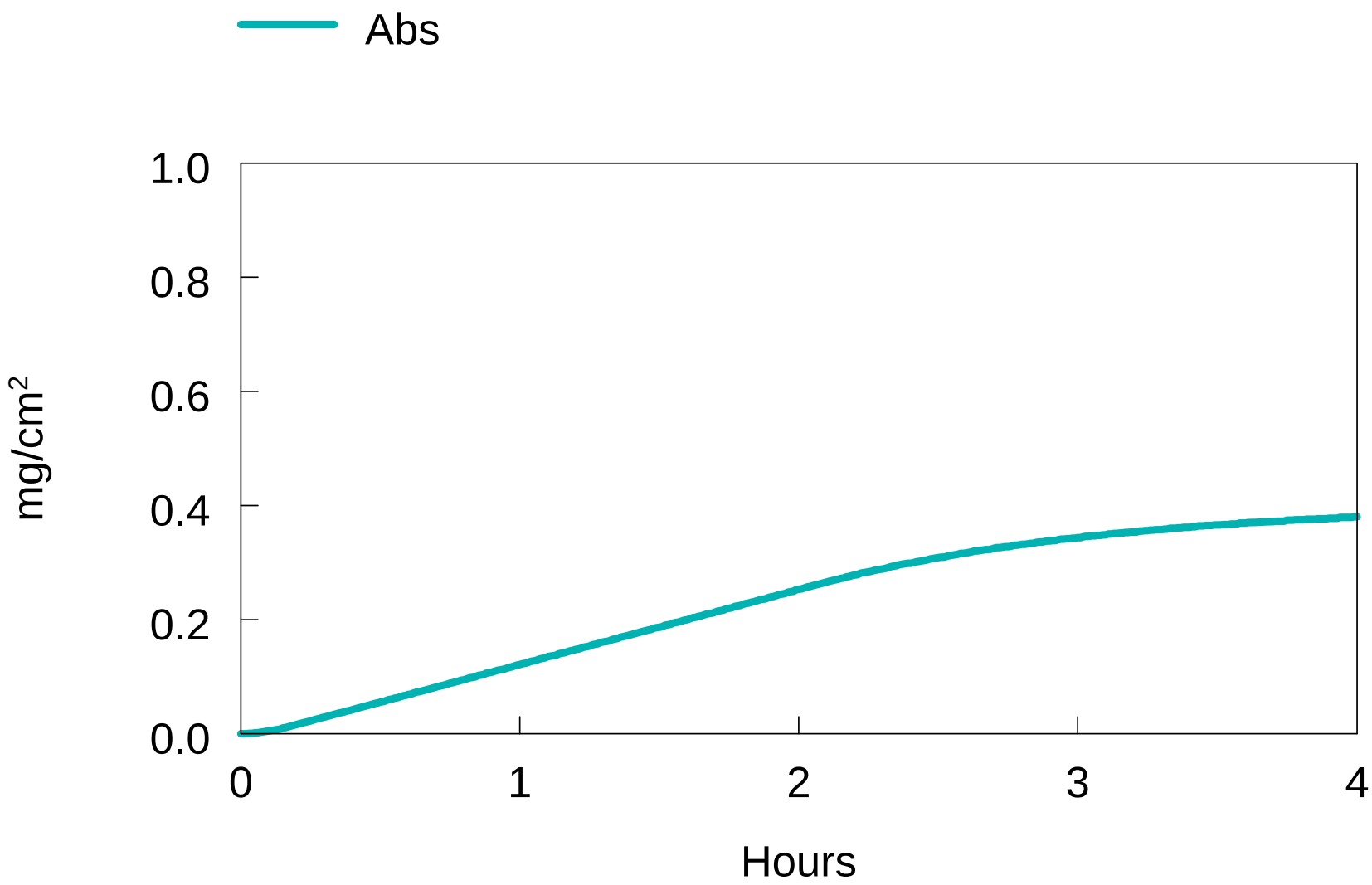
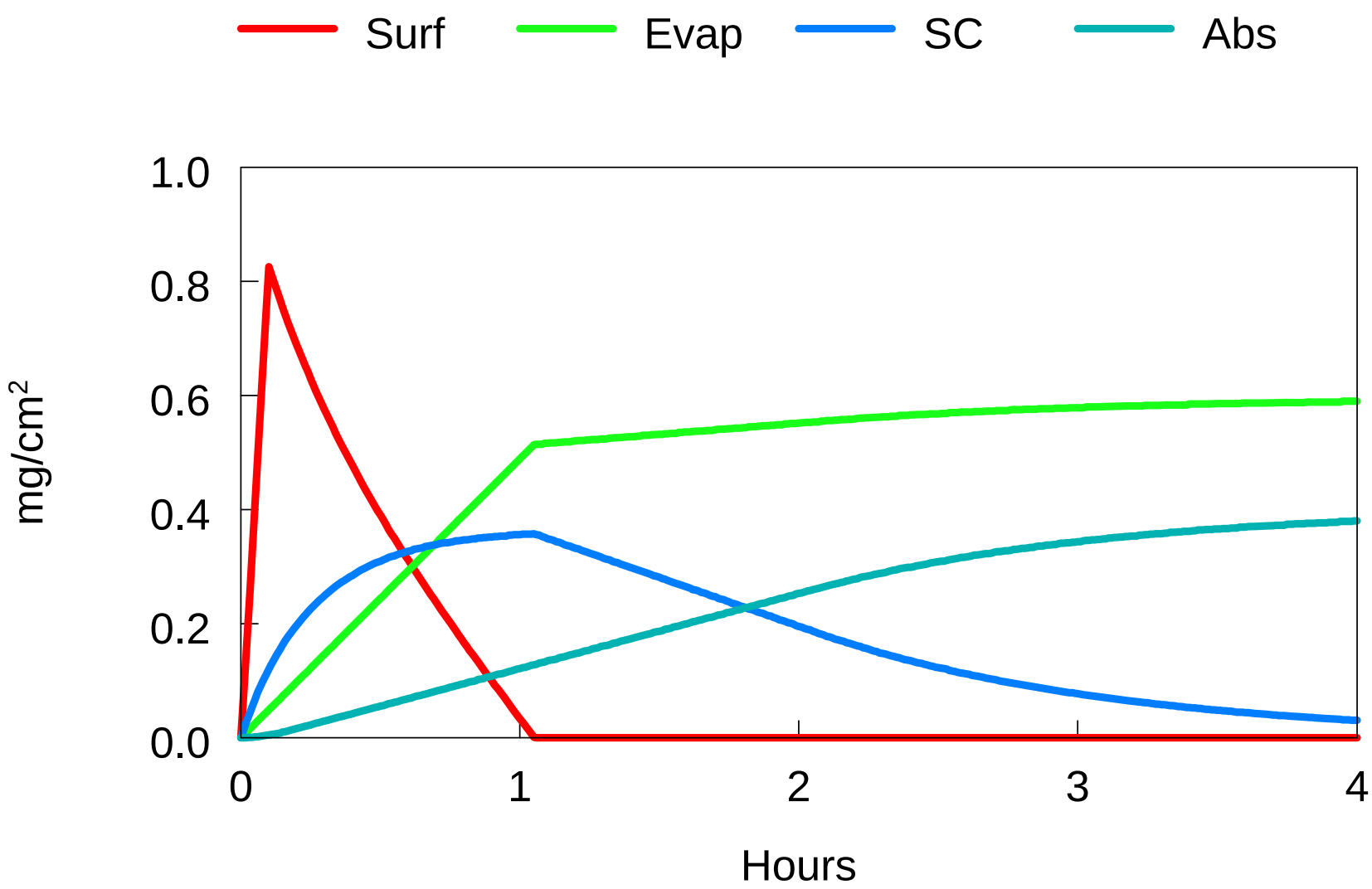


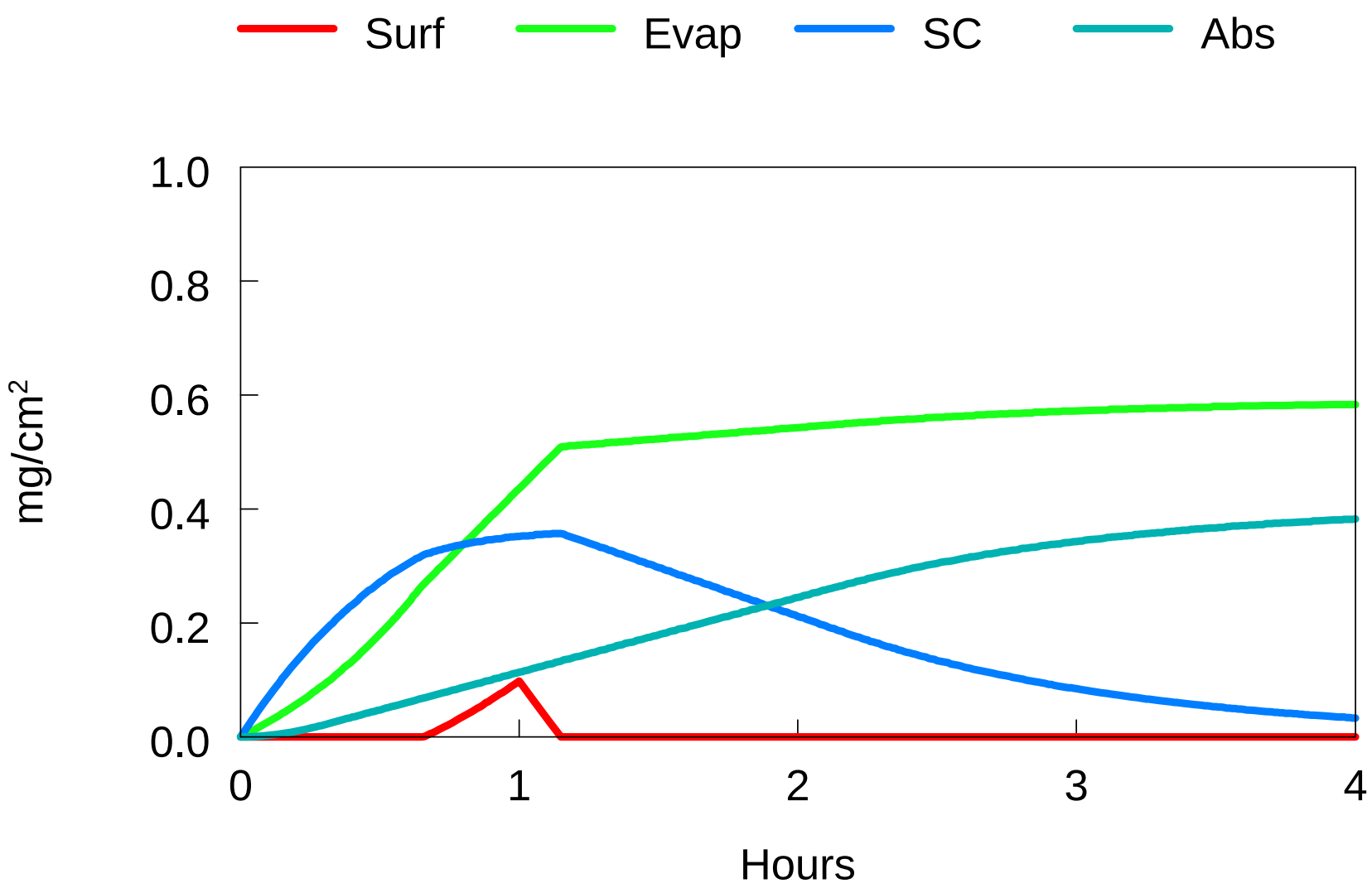
Deposition of benzylalcohol (1mg/cm^2 in 6 min)



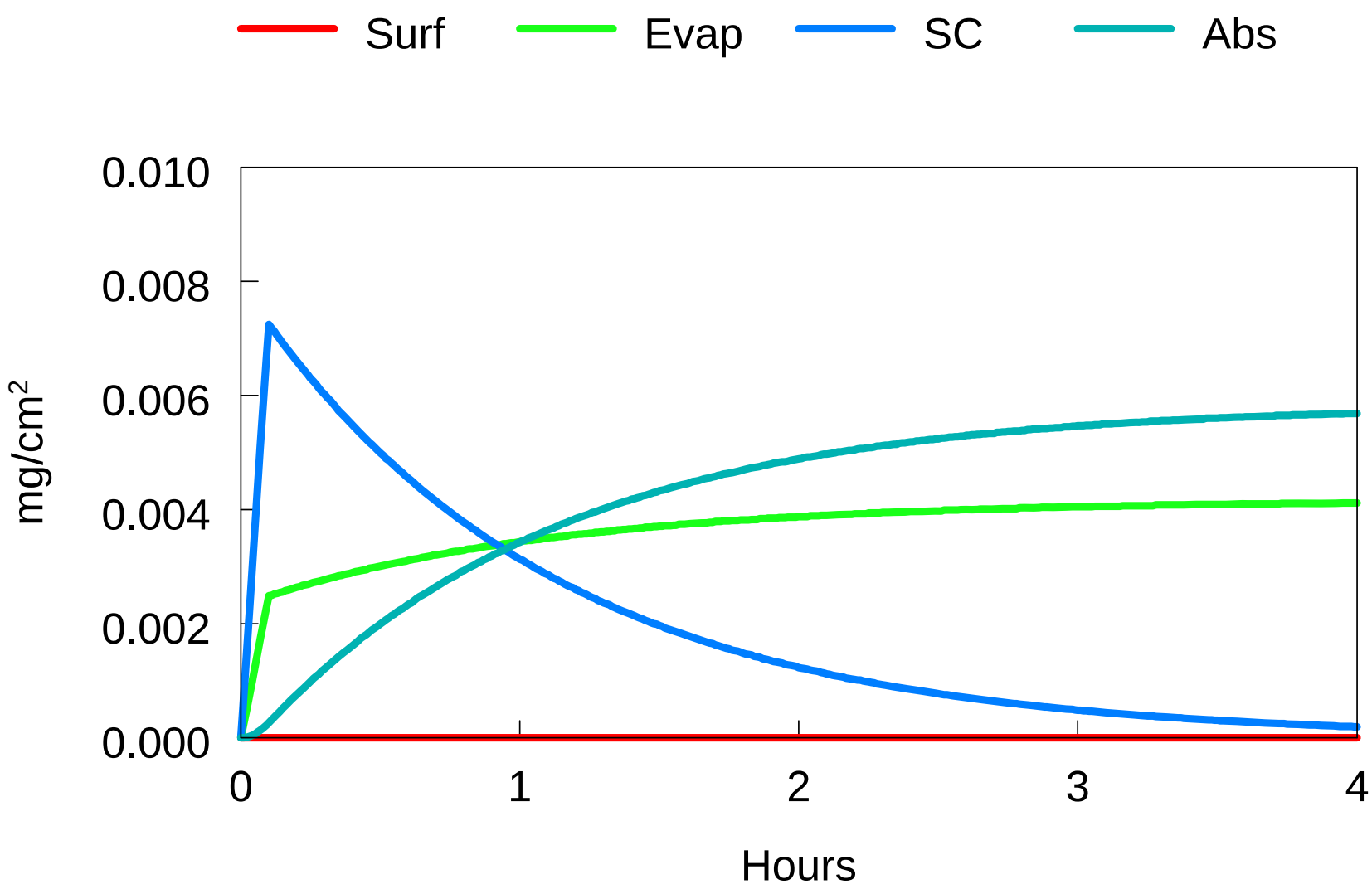
Deposition of benzylalcohol (1mg/cm^2 in 6 min)



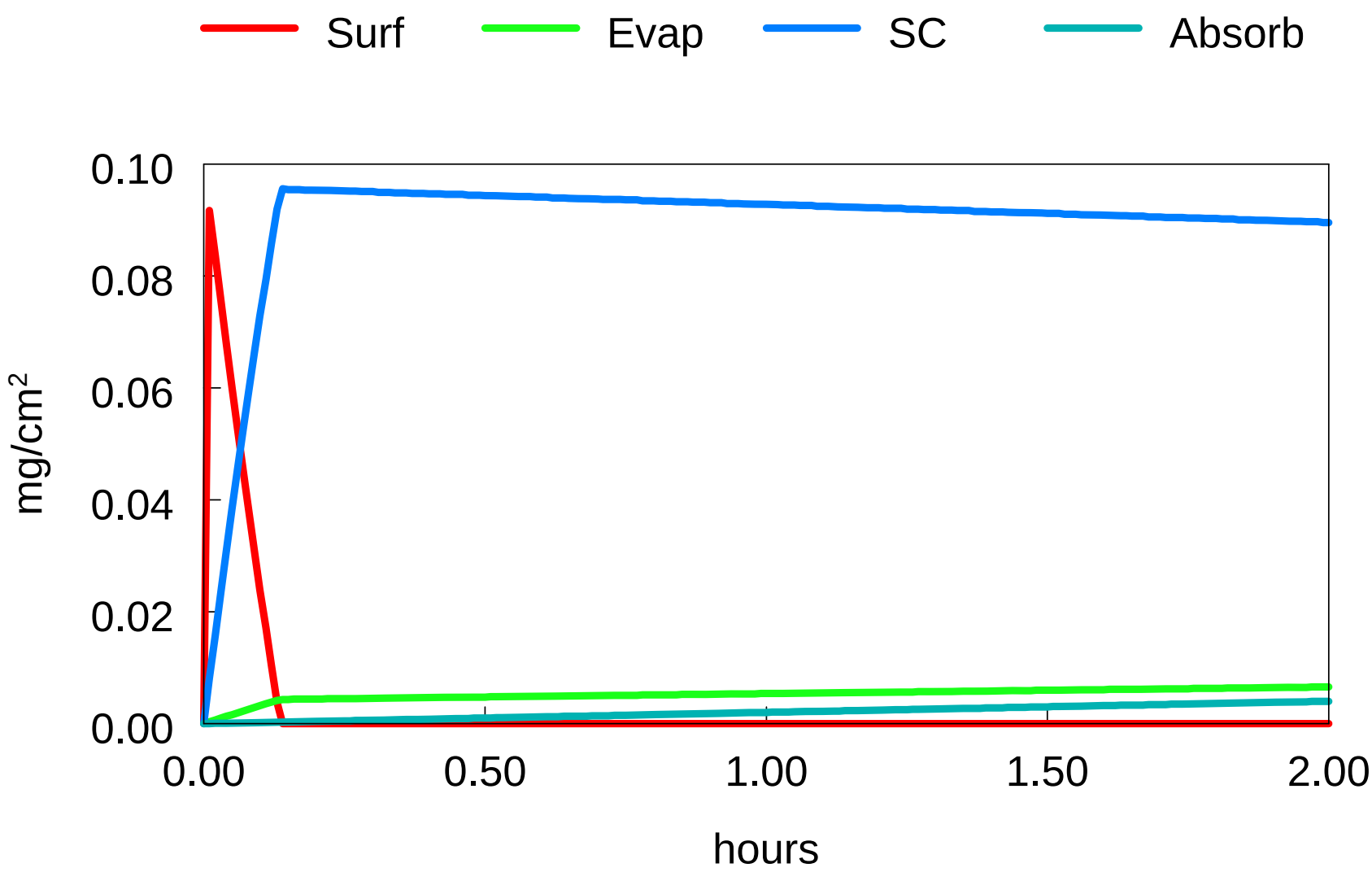
Deposition of benzylalcohol (1 mg/cm^2 in 1 hour)



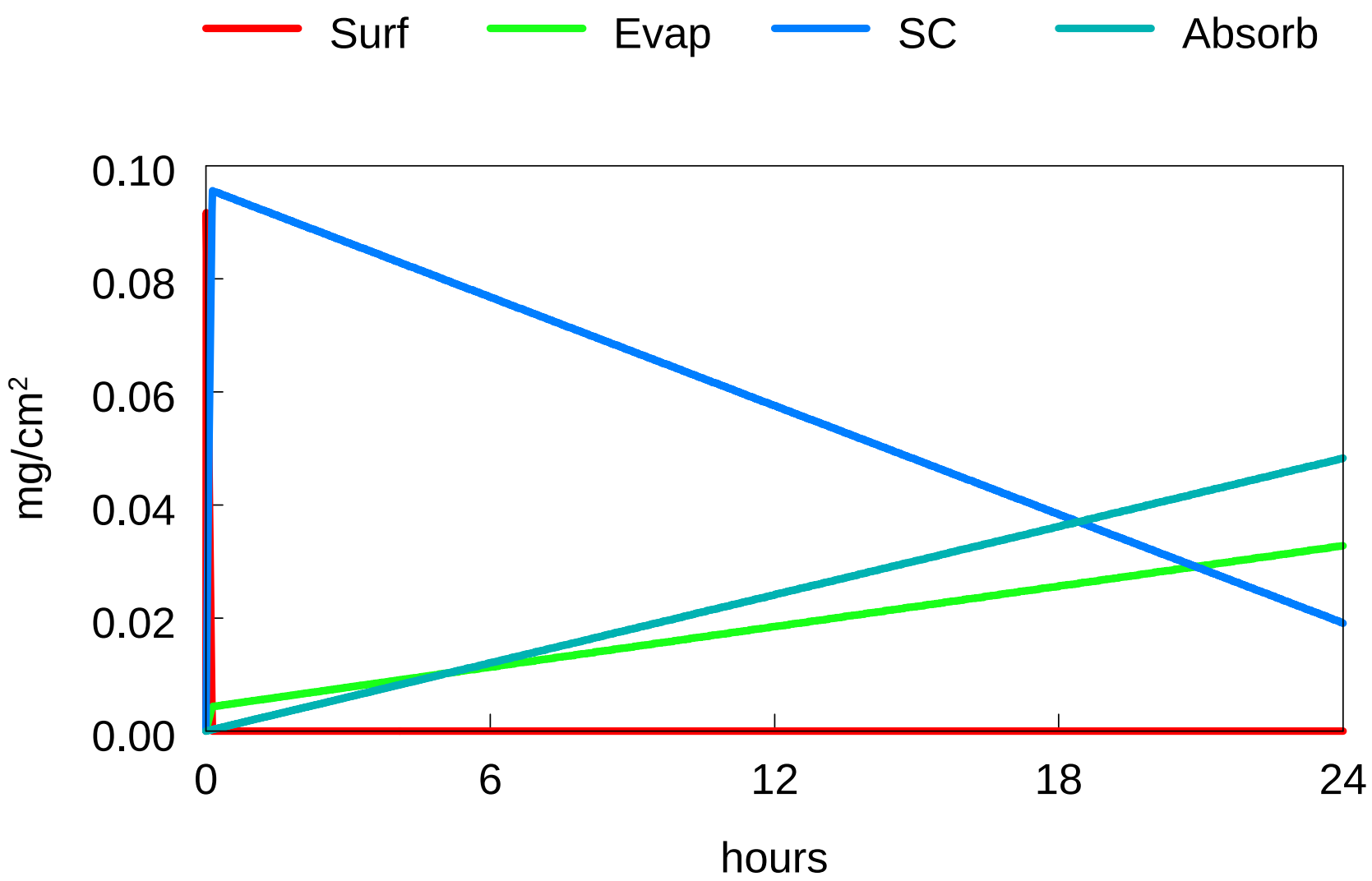
Deposition of benzylalcohol (10 µg/cm^2 in 6 min)



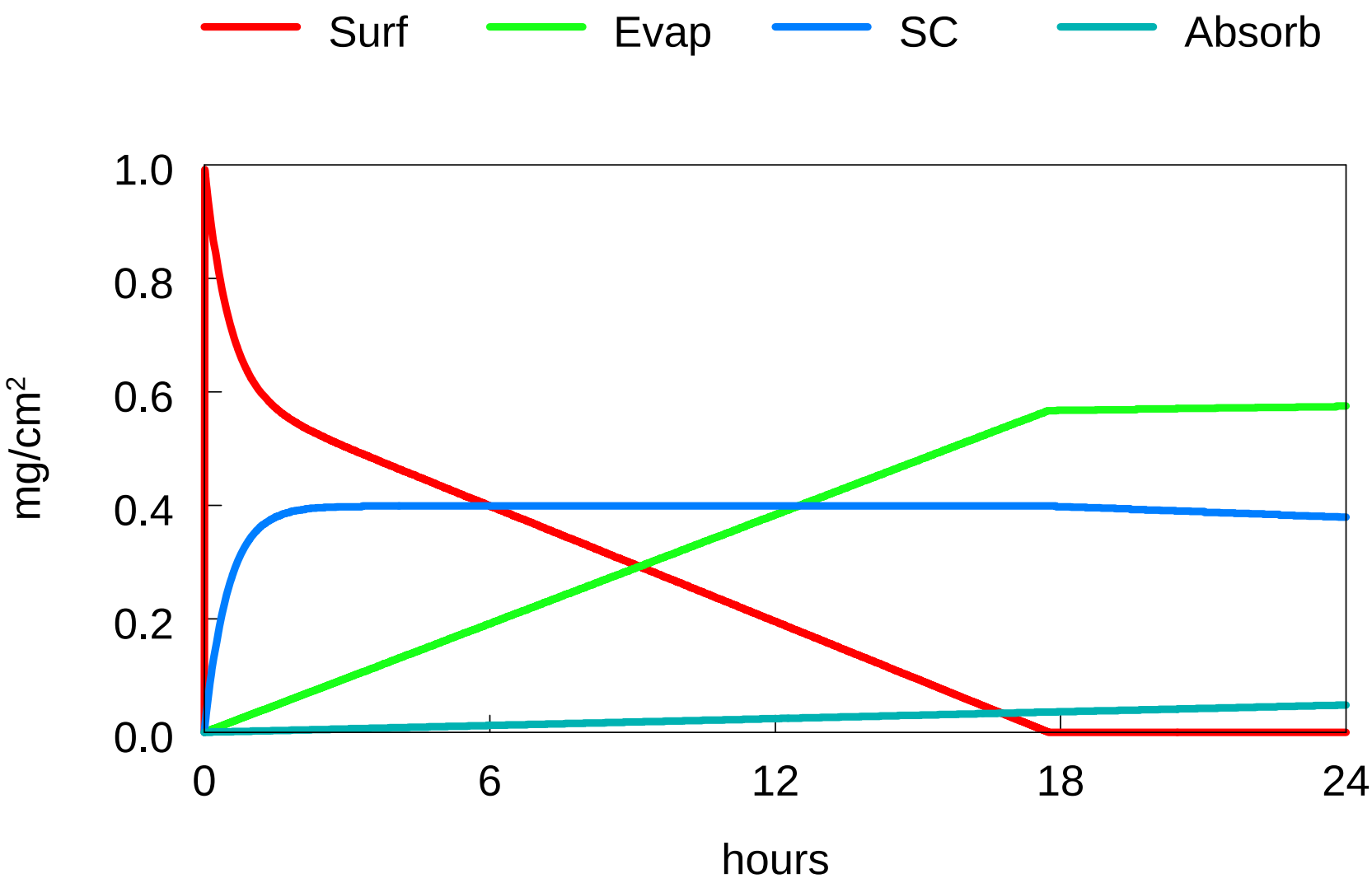
Application of DEET (0.1mg/cm^2)



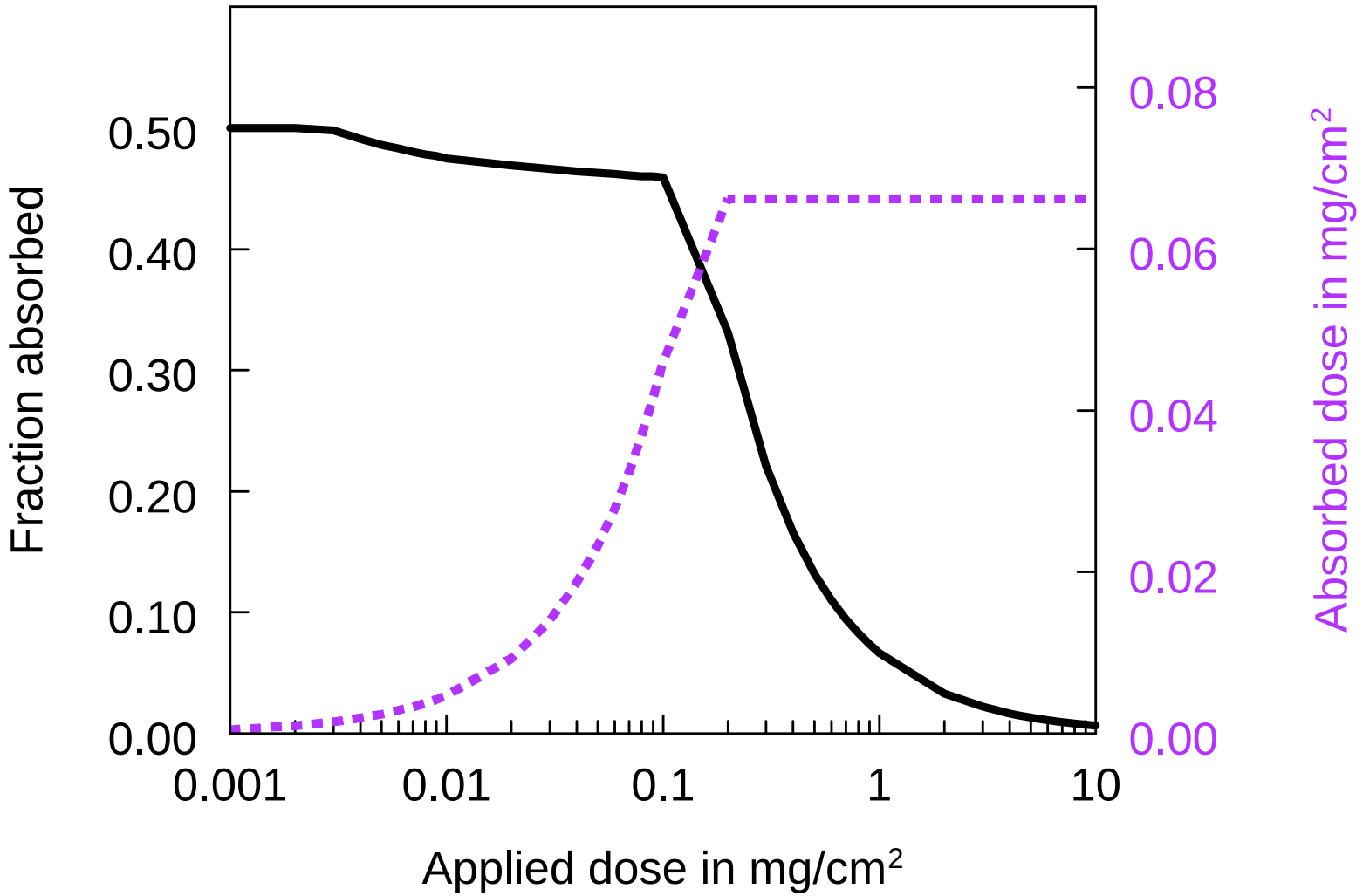
Application of DEET (0.1mg/cm^2)



Application of DEET (1mg/cm^2)



Single application of naphthalene on skin
Absorbed dose after 24 hours



Conclusions

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