

Background Generic PBPK-model

IndusChemFate

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CEFIC-LRI-project

Purpose of IndusChemFate (1)

- Guesstimate of concentration of parent and of metabolites in exhaled air, blood , urine and organ tissues as a result of exposure by inhalation, by ingestion or by dermal absorption.
- Balance between minimum input data and maximum output information by making use of QSARs for estimating partition coefficients (blood/air and tissue/blood) of parent compound and its sequential metabolites (maximum 4)

Purpose of IndusChemFate (2)

Contribution to understand the process of absorption, distribution, metabolism and excretion of parent and metabolites by

- Plotting concentration of parent and metabolites in exhaled air, blood and urine, resulting from exposure, against the time of observation after the start of exposure.
- Making a mass balance of parent absorbed and parent and metabolites excreted.

Focus on man (TGD 2nd Edition)

- Bodyweight 70 kg
- Number of 11 organs
- Human organ weight
- Blood flow through organs
- Alveolar volume
- Ingestion
- Skin surface (18000 cm² for vapour, 1000 cm² for liquids)

Description of ADME

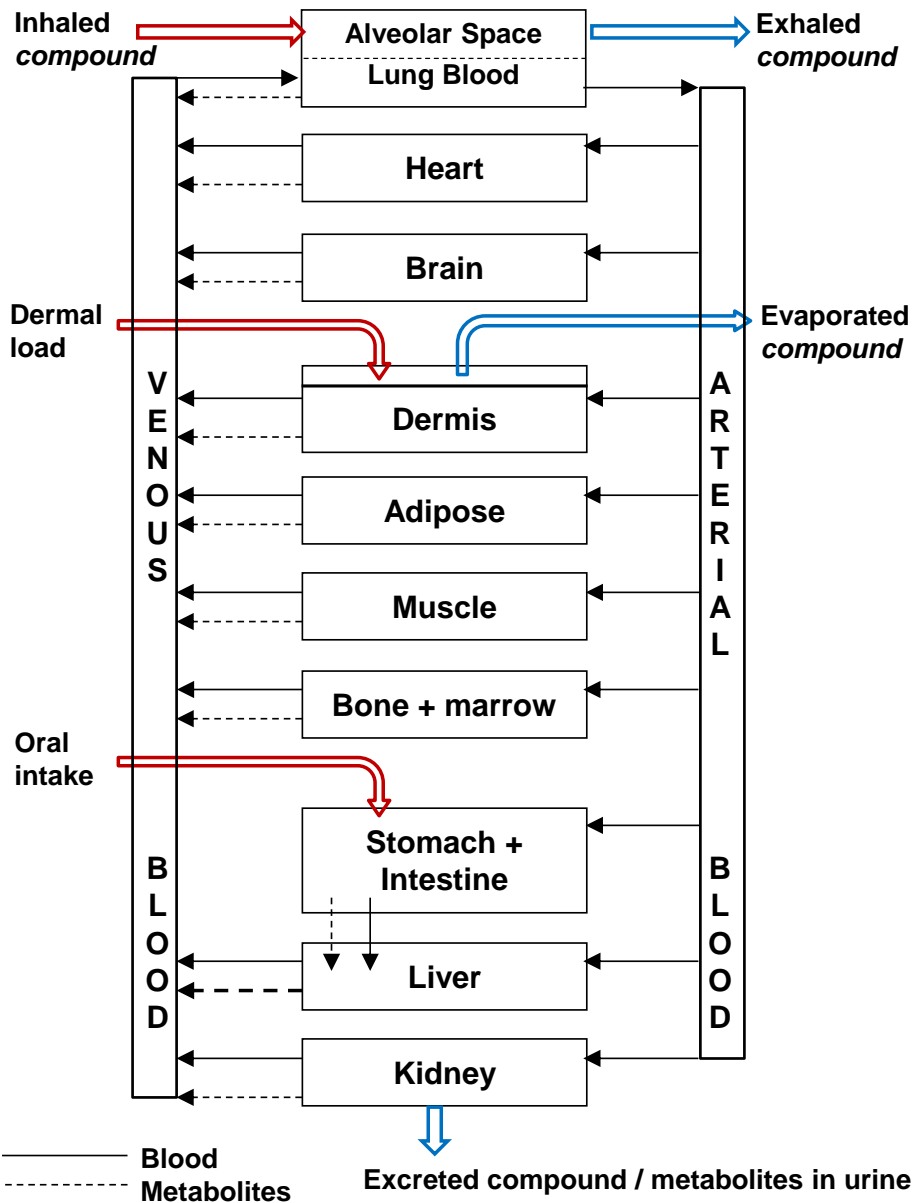
- Absorption
 - Inhalation (blood/air partitioning QSAR)
 - Skin from solid or liquid (QSAR)
 - Skin from vapour in air (QSAR)
 - Ingestion (dose released to intestinal tissue)
- Distribution
 - blood/organ tissue partitioning (QSAR)

Inhalation(blood/air partitioning)

- Assumed equilibrium between alveolar air and blood
- Equilibrium controlled by blood/air partition coefficient
- Blood to be considered as a water compartment and a lipid compartment
- QSAR for blood/air partition coefficient , controlled by dimensionless Henry coefficient and octanol/air partition coefficient (Meulenbergh & Vijverberg 2000)

Distribution parameters

- Blood flow, blood volume and organ volume
- Tissue/blood partition coefficients
- QSAR on the basis of:
 - Log(octanol/water partition coefficient)
 - water and lipid compartment in blood and organ
 - partitioning between blood and organ on the basis of the fraction of lipids
 - DeJongh, Verhaar & Hermens (1997)



Metabolism (parent + 4 metabolites)

- Simulation in all organs (optional)
- Default in liver
- Distinction removal/production specific metabolites
- Phase 1 and phase 2 reactions
- Vmax and Km from literature, presented as
- Vmax in ng/min/mg microsomal protein)
- One gram of liver tissue contains 50 mg/microsomal protein (15th ECVAM report, Blaauboer et al. 1996)

Distinction removal and production

- Parent compound might be biotransformed into more than one metabolite in the liver.
- Removal of parent is described by an overall V_{max} and K_m , reflecting all biotransformations.
- Production of a specific metabolite is described by the corresponding specific V_{max} and K_m (benzene, phenol, muconic acid, phenylmercapturic acid)

Enterohepatic circulation

- Some phase 2 metabolites (glucuronides) might be leave the liver via bile excretion into the intestines.
- The metabolite is reabsorbed from the intestines and transferred to the liver via the portal vein.
- IndusChemFate simulates this enterohepatic circulation by setting the removal via bile as ratio of the removal via the liver venous blood. If the fraction is set to 1, 50% of the metabolite is removed via bile and 50% is removed via venous liver blood.

Excretion via kidney (parent + metabolites)

- Arterial flow (30%) generates glomerulus filtrate
- Only water soluble fraction in blood considered
- Tubular resorption to be set
 - 'y' means 99% tubular resorption, 1% excretion
 - 'n' means 0 % tubular resorption, 100% excretion
 - '?' simple rule
 - logKow (at pH 7.4) < -1.5 means 100% excretion
 - logKow (at pH 7.4) => -1.5 means 1% excretion

Addition to classic PBPK-model

- Most PBPK-models consider only absorption by inhalation and ingestion.
- Dermal absorption is mostly modelled as fraction of the applied amount per day.
- IndusChemFate considers dermal absorption through
 - total body surface as vapour in ambient air.
 - limited skin surface of hands and underarms by direct skin contact with neat liquids and solids dependent
- IndusChemFate introduces a skin PBPK-model.

Exposure via skin

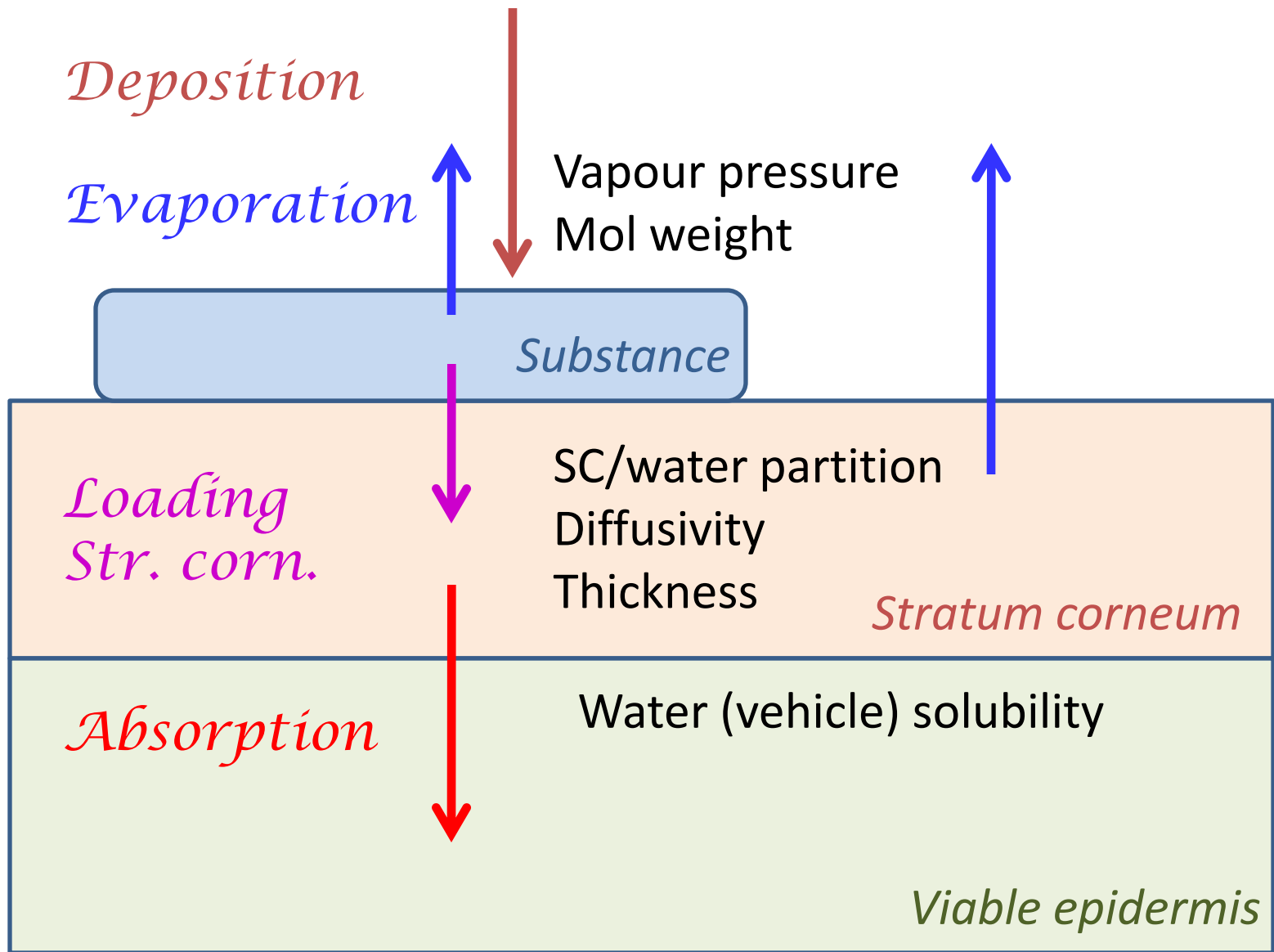
- Absorption via the vapour phase. The vapour permeation coefficient is derived from the aqueous permeation coefficient, the Henry coefficient and the diffusivity in air
- Absorption from deposited liquids or solids of neat substance on the skin. This requires a more complex approach (skin PBPK-model)

Starting points of SkinPerm(1)

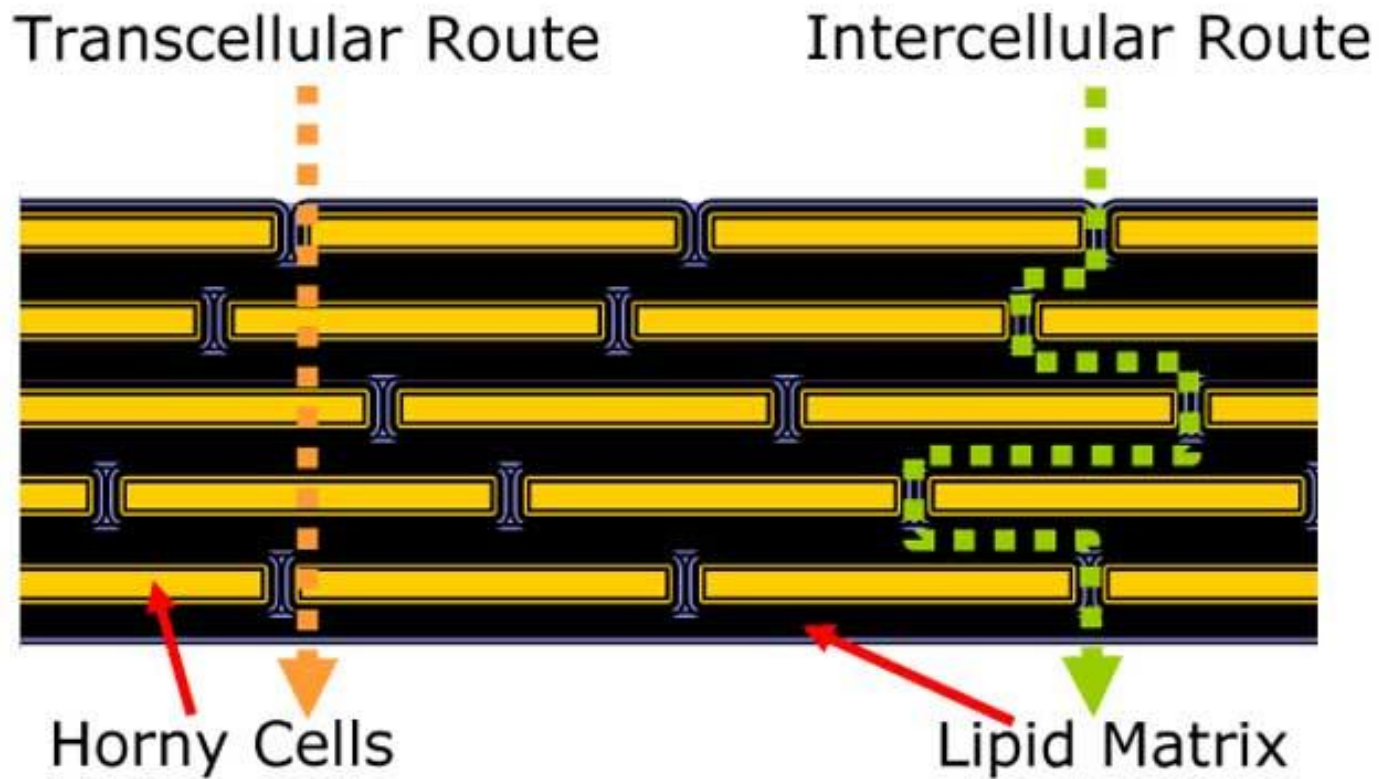
- A guesstimate of systemic absorption from dermal exposure to substances
- by using simple retrievable information:
 - molecular weight
 - water solubility (mg/litre)
 - vapour pressure (Pascal)
 - **log(octanol/water) at pH 5.5 (skin pH)**
 - density (mg/cm³)

Log(Kow) at different pH

- Nicotine CAS 54-11-5 (tertiary amine)
 - ACD/labs $\log(Kow) = 0.72$ (aqueous solution)
 - ACD/labs $\log(Kow) = -2.07$ (aq. at pH 5.5)
 - ACD/labs $\log(Kow) = -0.47$ (aq. at pH 7.4)
- Acetic acid CAS 64-19-7
 - ACD/labs $\log(Kow) = -0.29$ (aqueous solution)
 - ACD/labs $\log(Kow) = -1.07$ (aq. at pH 5.5)
 - ACD/labs $\log(Kow) = -2.86$ (aq. at pH 7.4)



Dermal permeation process (Cognis Skin Care Forum)



Starting points of SkinPerm(2)

- by using simple assumptions:
 - K_{aq} = Aqueous skin permeation coefficient (QSAR)
 - $\text{Log}(K_{ow})$, M_w (ten Berge 2009)
 - P_{sw} = Skin/water partition coefficients (QSAR)
 - $\text{Log}(K_{ow})$ (minimum -1.38) (ten Berge 2009)
 - Skin permeation coefficient neat substance
= K_{aq}/P_{sw}
 - Maximum absorption in SC is $0.4 \mu\text{l}/\text{cm}^2$

Starting points of SkinPerm(3)

- by using simple assumptions:
 - estimate maximum mass in SC in equilibrium with a saturated aqueous solution (= M_{aq})
 - M_{sc} is the actual mass in stratum corneum
 - postulate that,
 - the systemic absorp. rate is related to M_{sc}/M_{aq}
 - the systemic absorp. rate is maximum at $M_{sc} \geq M_{aq}$

Starting points of SkinPerm(4)

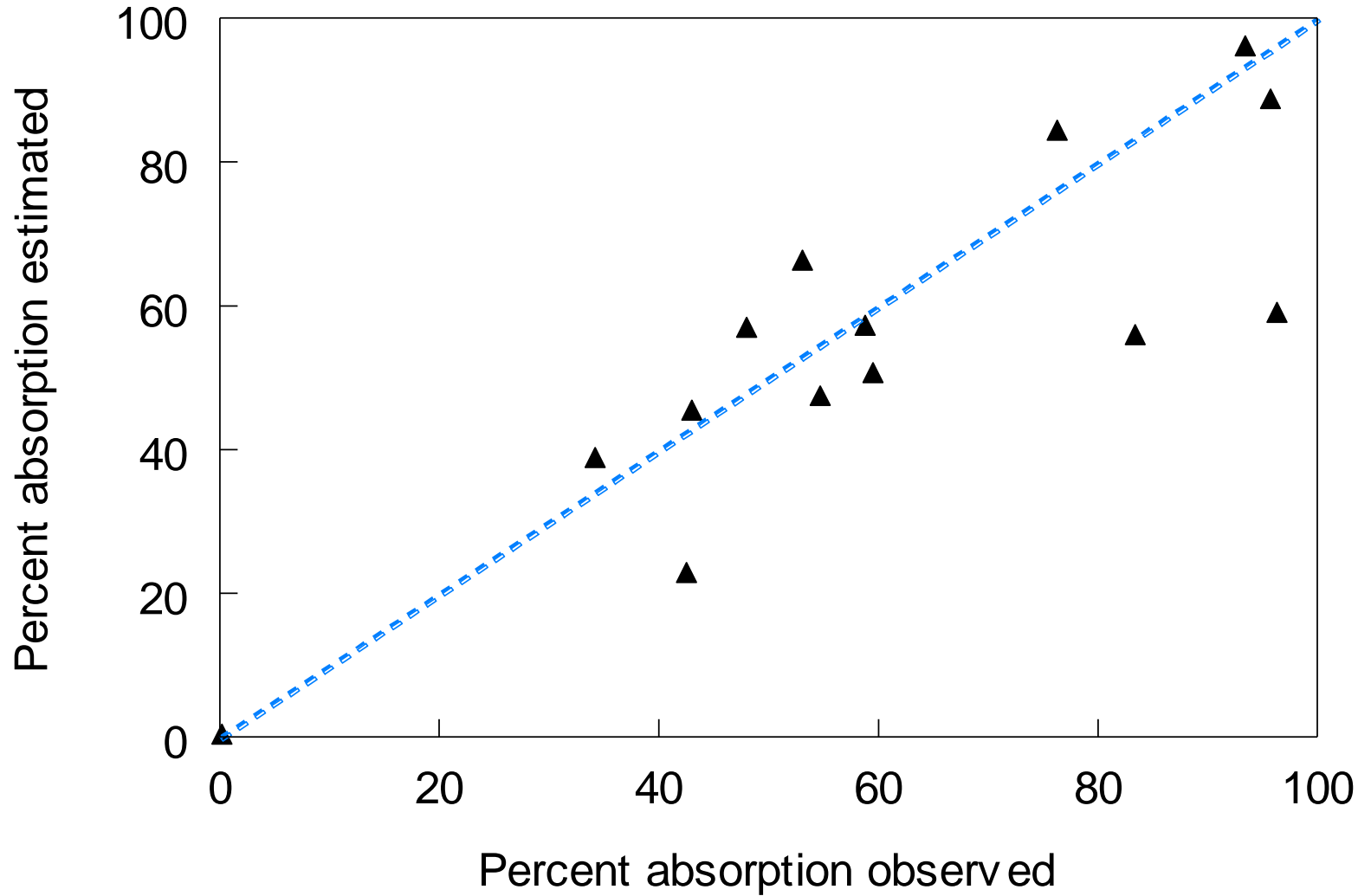
- by using simple assumptions:
 - estimate evaporation from substance layer on the skin according to REACH Guidance App R14.1
 - evaporation rate from stratum corneum related to Henry coefficient and aqueous perm.coeff. K_{aq}
 - the evaporation rate is related to M_{sc}/M_{aq}
 - the evaporation rate is maximum at $M_{sc} \geq M_{aq}$

Evaporation of non-occluded skin doses

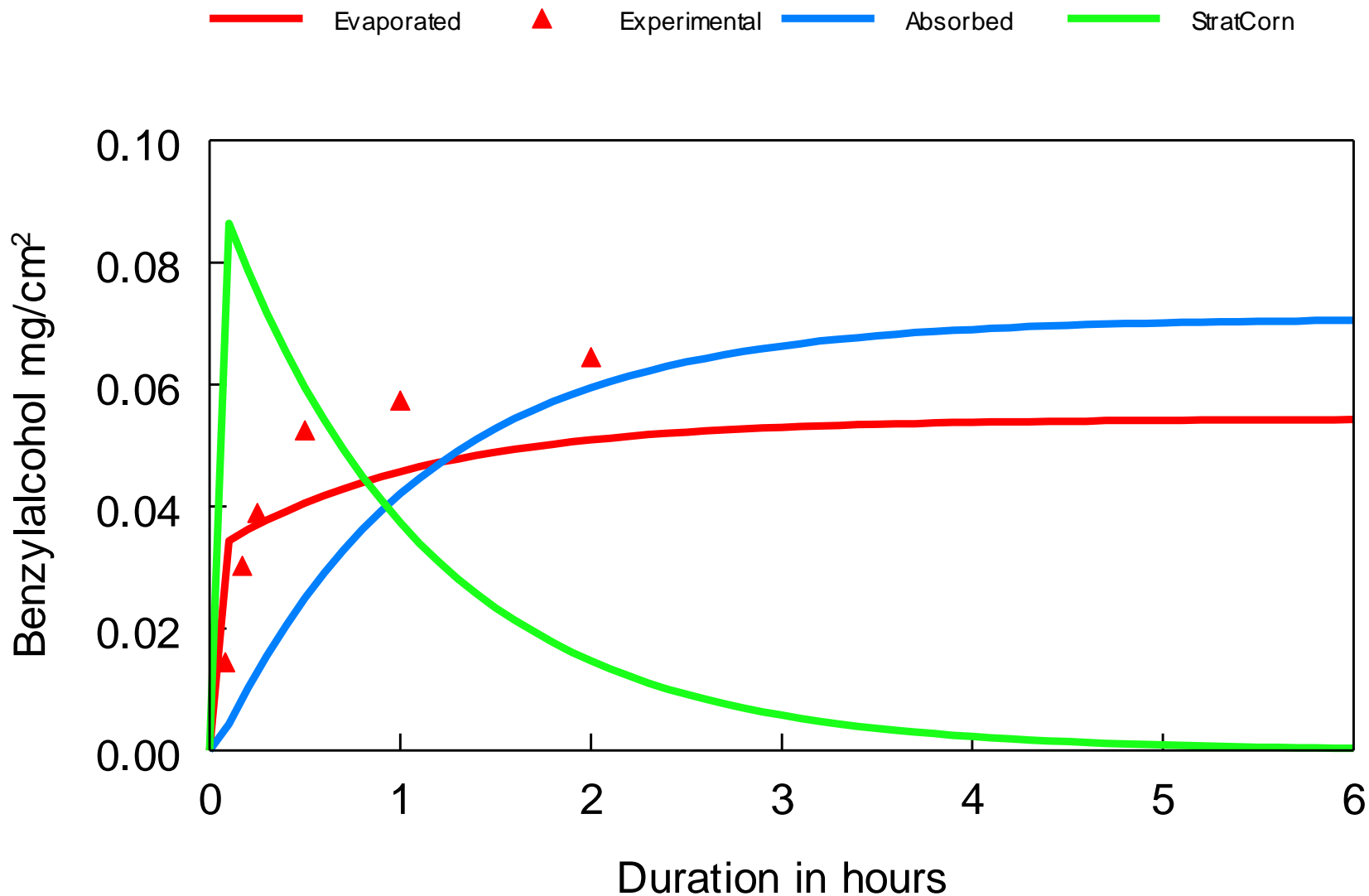
- Modjtahedi & Maibach (2008) **Benzeen**
- Sayasombati & Kasting (2004) **Benzylalcohol**
- Vuilleumier, Flament & Sauvegrain (1995)
12 perfume ingredients in alcohol
- Kasting & Saiyasombati (2001)
Evaluation Vuilleumier et al. (1995)

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

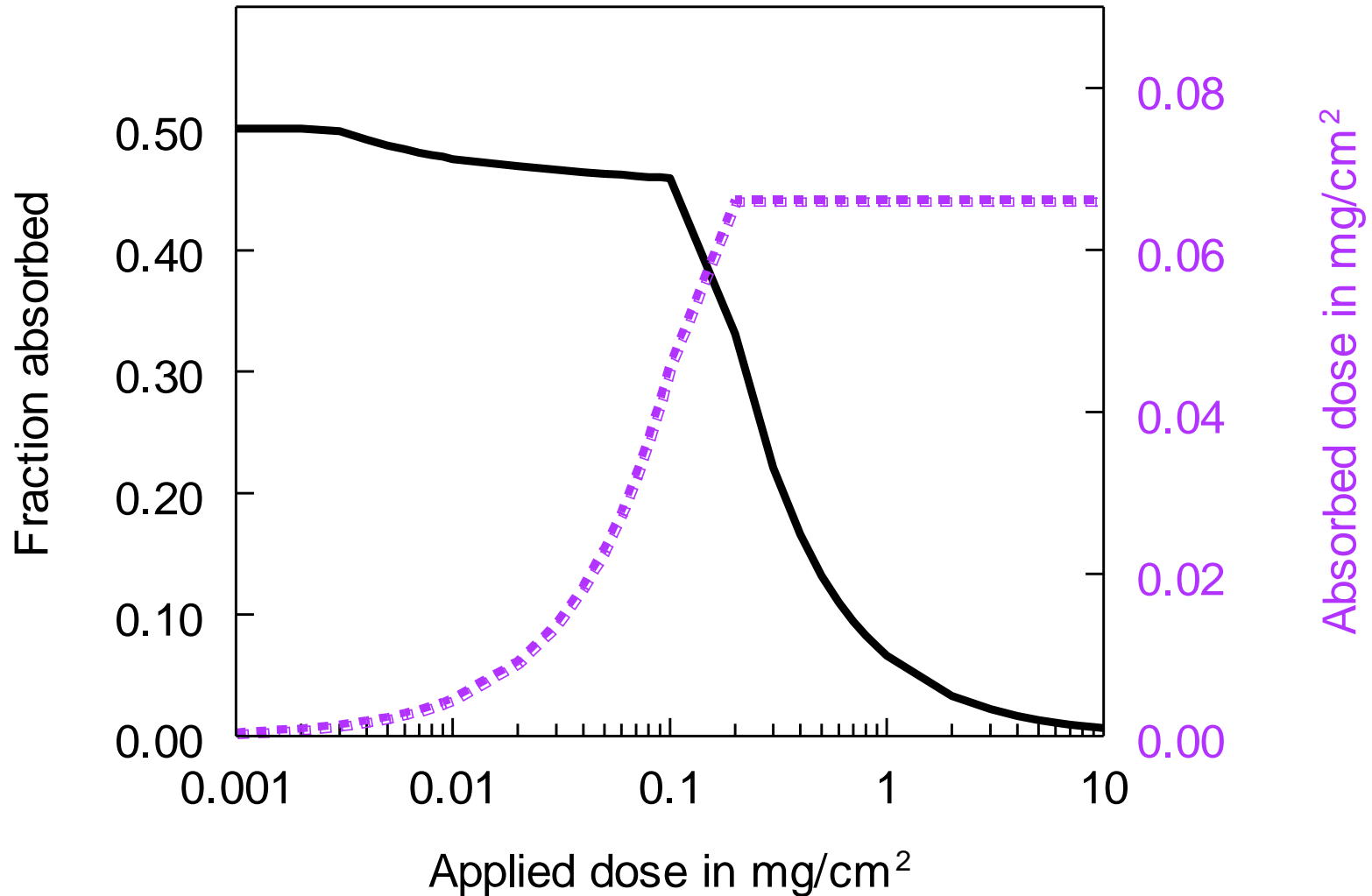


Dermal absorption of 0.125 mg/cm² benzylalcohol



Single application of naphthalene on skin

Absorbed dose after 24 hours



Conclusions on model of skin absorption

- Simulation of evaporation from and absorption through the skin was done on the basis of QSARs and physical behaviour
- Simulations were in line with experimentally observed evaporation and absorption
- This method is useful for risk assessment of dermal absorption of industrial chemicals (REACH)

Mass balance of absorption and excretion

- The PBPK-model puts together the absorption of the parent compound by inhalation, ingestion and skin absorption via vapour and via contact with the neat liquid.
- The sum of the absorbed mass of the parent should be equal to the sum of parent and metabolites, remaining in the body and excreted at any point in time from the start of exposure

Complexity of mass balance (MTBE)

Part.Coeff	MTBE	TBA	MPD	HIBA
Blood/Air	2.15E+01	1.21E+03	9.78E+04	1.07E+09
Adipose tissue/Blood	8.28E+00	2.03E+00	3.00E-01	1.00E-01
Bone/Blood	9.06E-01	7.93E-01	7.51E-01	7.39E-01
Brain/Blood	1.15E+00	9.48E-01	8.30E-01	7.75E-01
Heart/Blood	9.06E-01	7.93E-01	7.51E-01	7.39E-01
Kidney/Blood	9.49E-01	8.46E-01	7.93E-01	7.71E-01
Intestine/Blood	8.03E-01	6.08E-01	5.35E-01	5.15E-01
Liver/Blood	8.03E-01	6.08E-01	5.35E-01	5.15E-01
Lung/Blood	9.06E-01	7.93E-01	7.51E-01	7.39E-01
Muscle/Blood	9.06E-01	7.93E-01	7.51E-01	7.39E-01
Skin/Blood	9.06E-01	7.93E-01	7.51E-01	7.39E-01
BoneMarrow/Blood	1.15E+00	9.48E-01	8.30E-01	7.75E-01

Final Considerations on IndusChemFate

- Concentration in exhaled air, blood, organs and urine of parent compound and its metabolites could be estimated as function of exposure to the parent via inhalation, ingestion and skin contact.
- Application domain is related to simple organic molecules causing highest exposure to workers
- Ionised chemicals belong to the application domain
- Skin absorption is not reliable, if the deposited substance is corrosive or irritant to the skin.