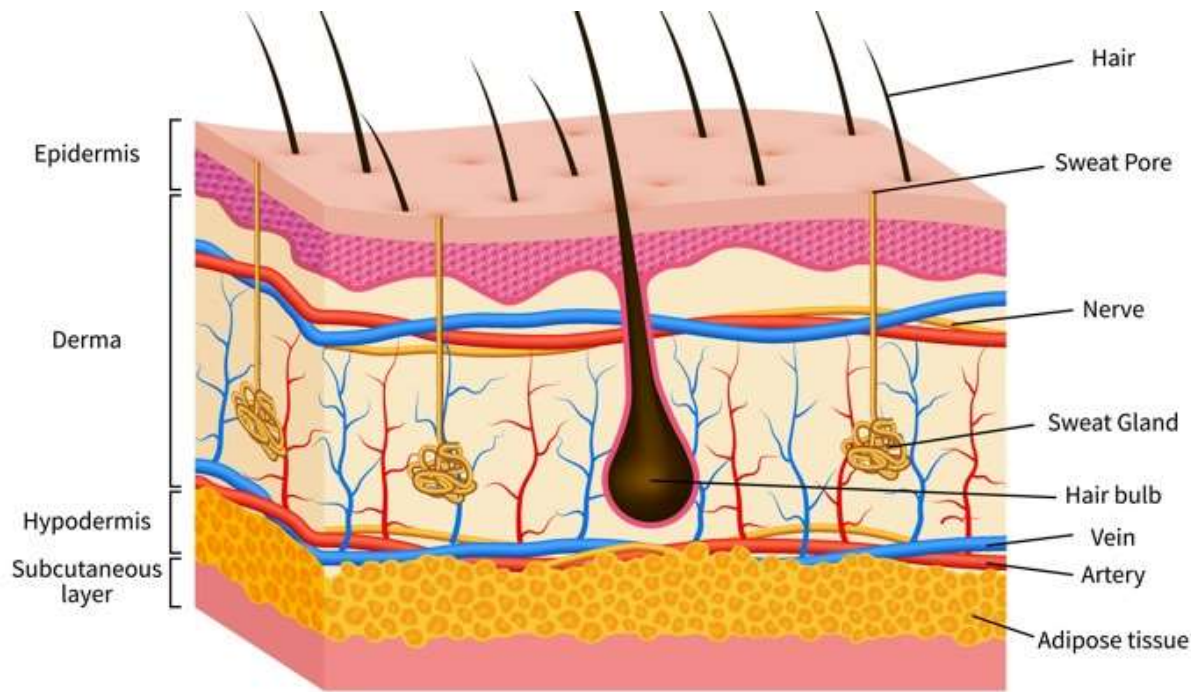


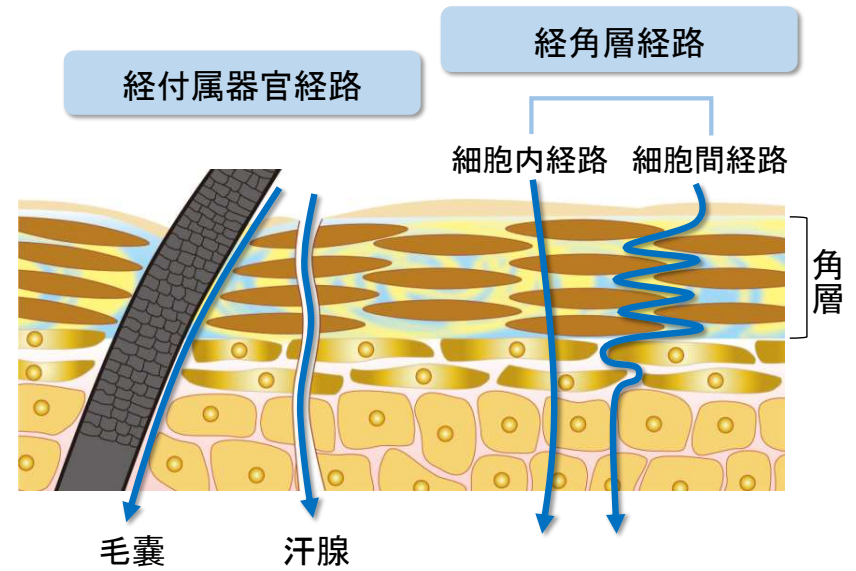
2層膜皮膚拡散モデルを用いた  
化学物質の経皮暴露後の吸収性  
*in silico*予測

城西大学 薬学部  
薬粧品動態制御学講座  
藤堂 浩明

# 皮膚の構造と皮膚浸透ルート



$C_v$ : 有効成分適用濃度  
 $K$ : 分配係数  
 $D_{sc}$ : 角層中拡散係数  
 $D_{AF}$ : 毛穴中拡散係数  
 $D_w$ : 水中拡散係数  
 $L$ : 膜の厚み



Drug Drug Drug

分配

拡散

$$\frac{dQ_2}{dt} = D_{AF} \cdot \frac{C_v}{L} = \frac{D_w}{\tau} \cdot \frac{C_v}{L}$$

Membrane 2 (M2)

Diffusion through solvent (usually water)-filled pores

Drug

分配

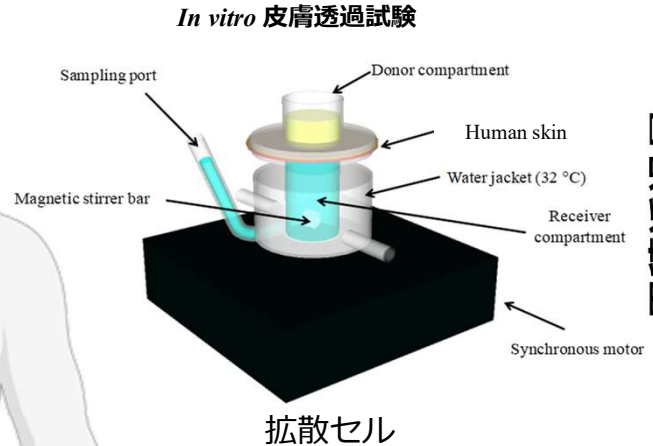
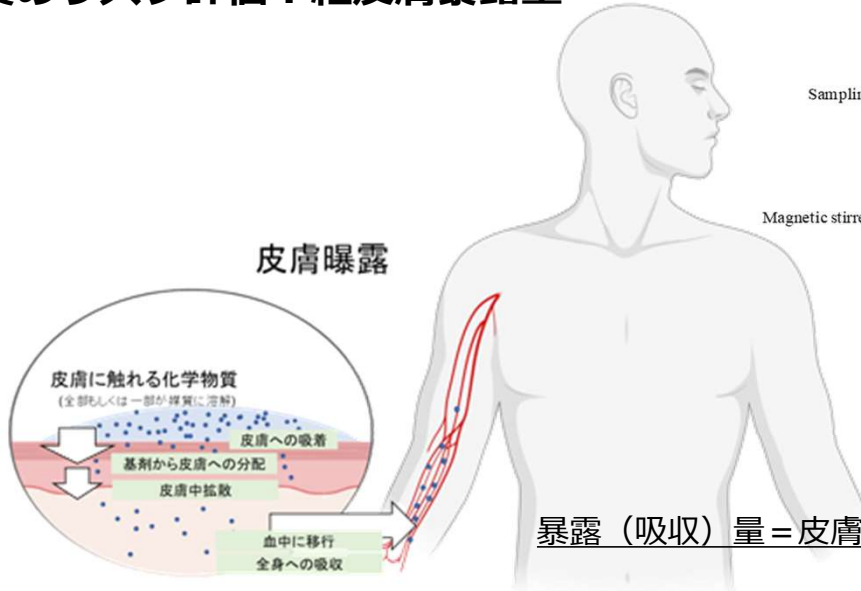
拡散

$$\frac{dQ_1}{dt} = D_{sc} \cdot \frac{KC_v}{L}$$

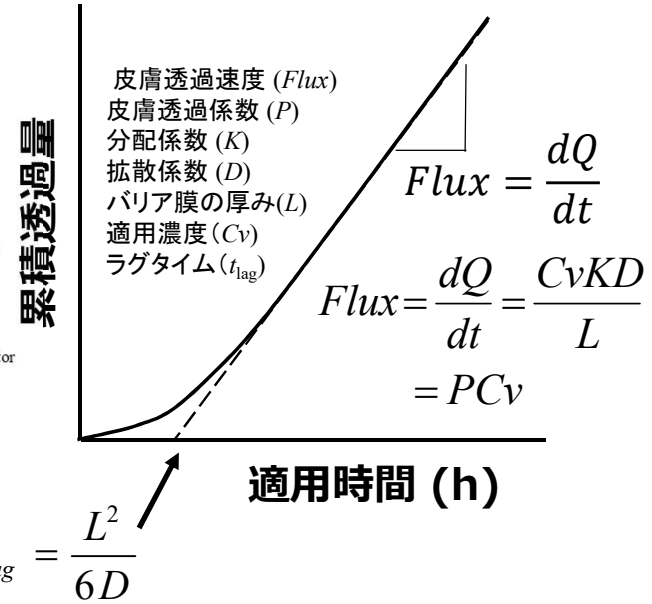
Membrane 1 (M1)

Diffusion through the homogeneous film

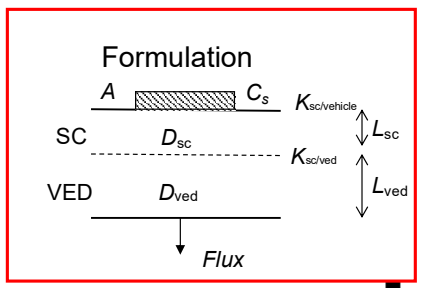
# 化学物質のリスク評価：経皮膚暴露量



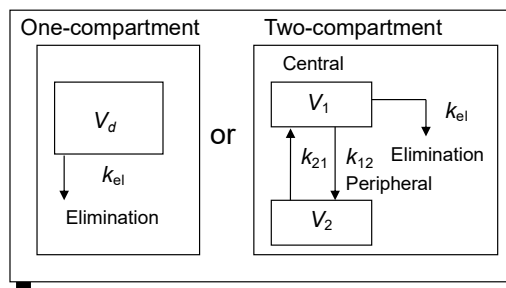
## 無限用量系 (物質濃度一定)



### In vitro skin permeation parameters

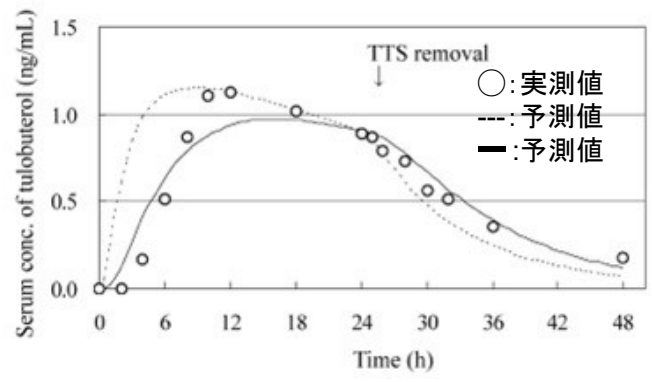


### Pharmacokinetic parameters



$$C_t = \frac{dQ/dt \cdot A}{V_d \cdot K_{el}} (1 - e^{-K_{el} \cdot t})$$

$dQ/dt$ : 皮膚透過速度 ( $\mu\text{g}/\text{cm}^2/\text{h}$ )  
 $A$ : 暴露面積 ( $\text{cm}^2$ )  
 $K_{el}$ : 消失速度定数 ( $\text{h}^{-1}$ )  
 $V_d$ : 分布容積 ( $\text{mL}$ )



Nakamura A., et al., *Chem Pharm Bull*, **60**, 300—305 (2012)

Prediction of blood concentration-time profile

# 化学物質の物理化学的パラメータを用いた皮膚透過パラメータの予測式

Potts & Guy \*1

$$\log P_{tot}(\text{cm/sec}) = -6.3 + 0.71 \times \log K_{O/W} - 0.0061 \times M.W.$$

$P_{tot}$ : 物質の皮膚透過係数

Data range:  $18 < M.W. < 765$ ,  $-3 < \log K_{O/W} < 6$

\*1 Potts & Guy., *Pharm. Res.*, **9**, 663-669 (1992).

Wang-Kasting-Nitsche (Wang 2007)

$$K_{SC/W} = 0.014(K_{O/W})^{0.81} + 0.782 + 1.381(K_{O/W})^{0.27} \text{ (fully hydrate)}$$

$K_{SC/W}$ : stratum corneum partition coefficient

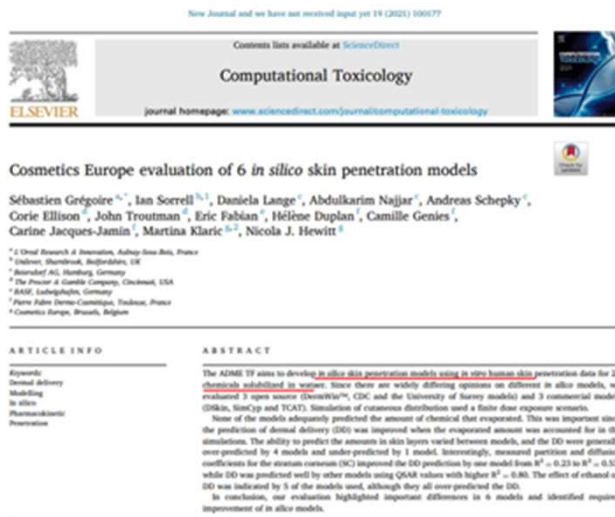
$$D_{SC} = \frac{(P_{SC/W})^{comp} h_{SC}}{K_{SC/W}}$$

$K_{O/W}$ : octanol/water partition coefficient

$D_{SC}$ : stratum corneum diffusivity

$h$ : thickness of the SC

$P_{SC/W}$ : permeability coefficient



S. Grégoire, et al., *Computational Toxicology*, **19**, 2021

## 無料

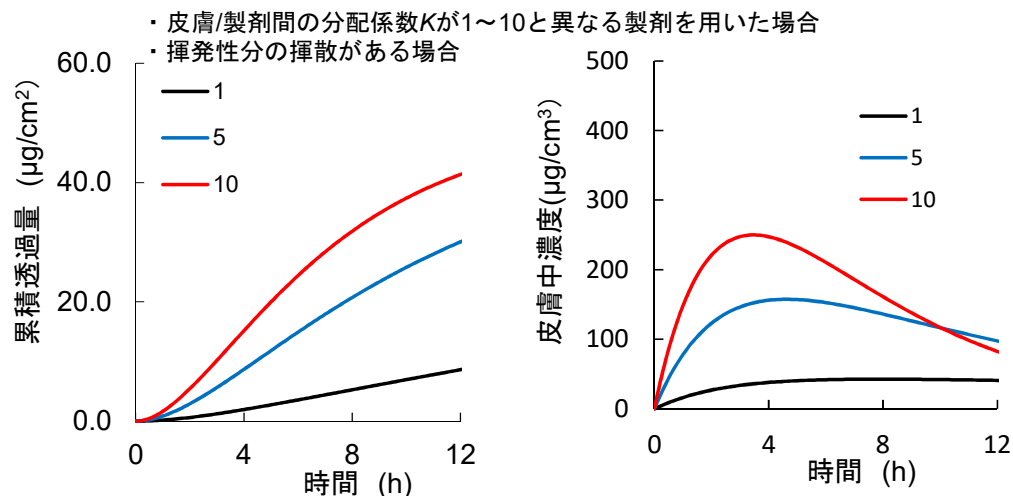
- アメリカ 疾病対策予防センター CDC model
- アメリカ合衆国環境保護庁 EPA Dermwin™
- サリー大学 Surrey model

## 有料

- Scientific Consilience Dskin
- Certara SimCyp Simulator software
- Simulations Plus
- GastroPlus™

# 有限用量系（濃度変化あり）で適用した物質の皮膚透過量-時間プロファイル予測が可能

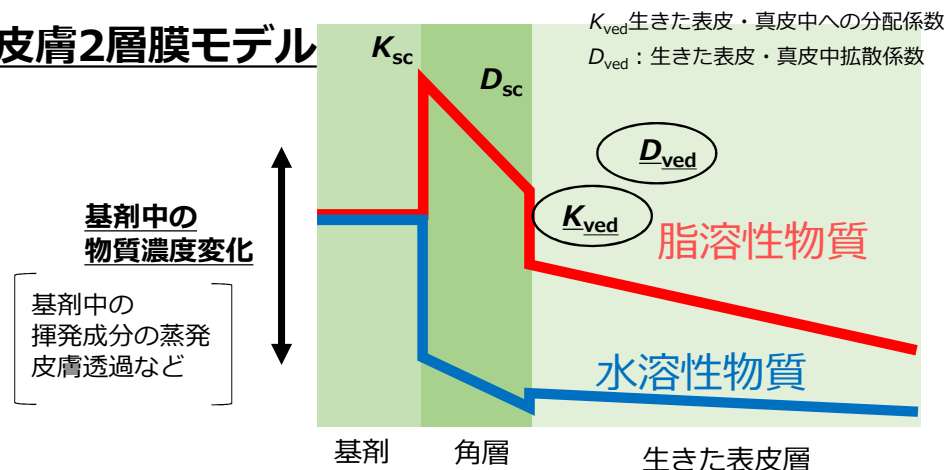
(皮膚透過パラメータ+適用物質の皮膚表面上での濃度変化)



藤井まき子., *日本化粧品学会誌*, **43**, 243-244 (2019)

暴露（吸収）量 = 皮膚透過量 + 皮膚中量

## 皮膚2層膜モデル

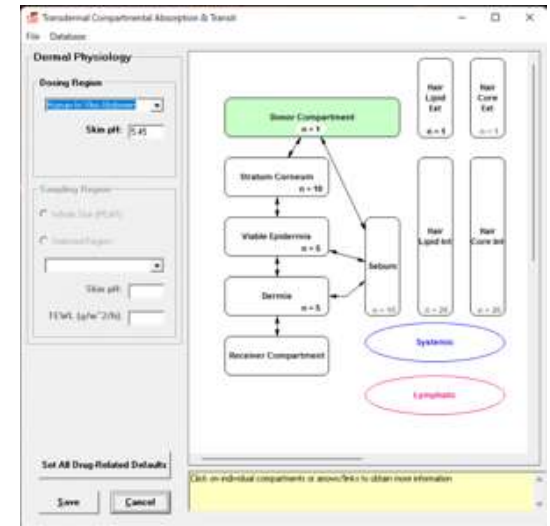




# GastroPlus® Dermal model (TCAT)

**入カパラメーター**  
**SMILES記法による分子構造式**  
**(分子量、油水分配係数)**  
**適用濃度**  
**適用容量**  
**飽和溶解度**  
**適用時間**

**入カパラメーター：蒸気圧**  
**溶媒密度**  
**溶媒分子量**



## Wang-Kasting-Nitsche (Wang 2007)

$$K_{SC/W} = 0.014 (K_{o/w})^{0.81} + 0.782 + 1.381 (K_{o/w})^{0.27} \text{ (fully hydrate)}$$

$$D_{SC} = \frac{(P_{SC/W})^{comp} h_{SC}}{K_{SC/W}}$$

$K_{SC/W}$  : stratum corneum partition coefficient

$D_{SC}$  : stratum corneum diffusivity

$K_{o/w}$  : octanol/water partition coefficient

## Kretsos (Kretsos 2008)

$K_{ved}$  : 固定値

$$K^{VE/W} = 0.7$$

$P_{sc/w}$  : permeability coefficient

$h$  : thickness of the SC

$K^{VE/W}$  : viable epidermis partition coefficient

$$D^{VE} \text{ (cm}^2/\text{s)} = 10 - 4.15 - 0.655 \log MW$$

$D^{VE}$  : viable epidermis diffusivity

## ✓ Volatilization

Nielsen

$$K_{sol}^{evap} = 0.662 D_{sol}^{air 2/3} v^{-1/6} u^{1/2} L^{-1/2} \left( \frac{P}{P - P_{sol}} \right)$$

$D_{sol}^{air 2/3}$  : Diffusivity of solvent in air

$p_{sol}$  : Vapor pressure of the solvent

$k_{sol}^{evap}$  : Evaporation rate constant

$u$  : Ambient air velocity

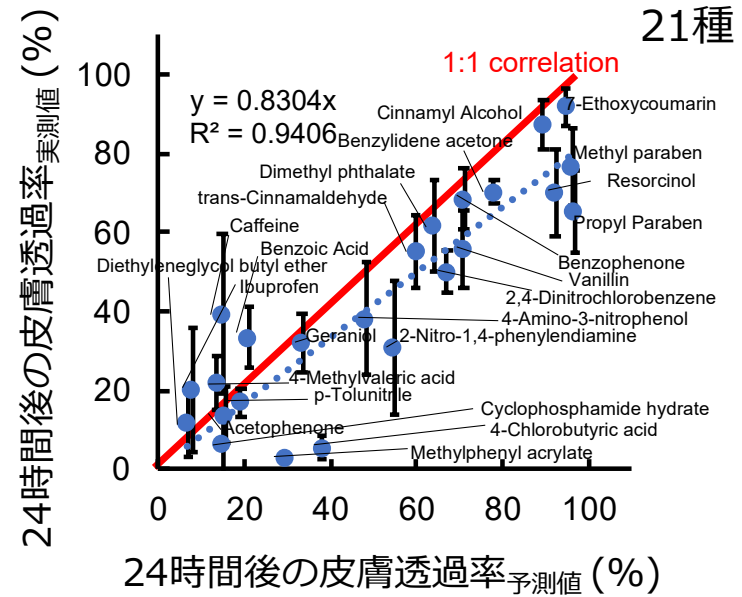
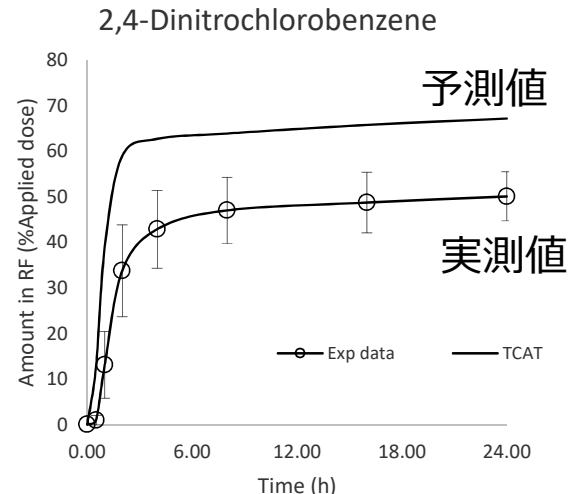
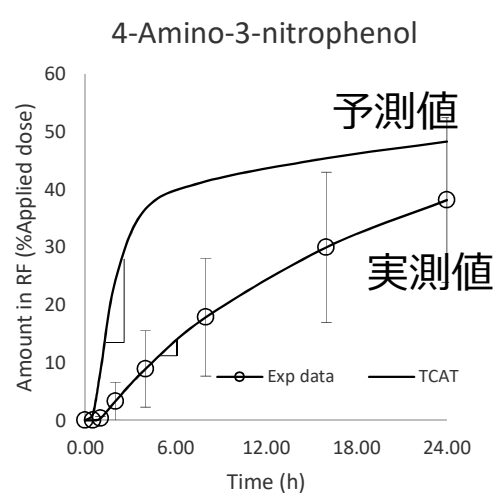
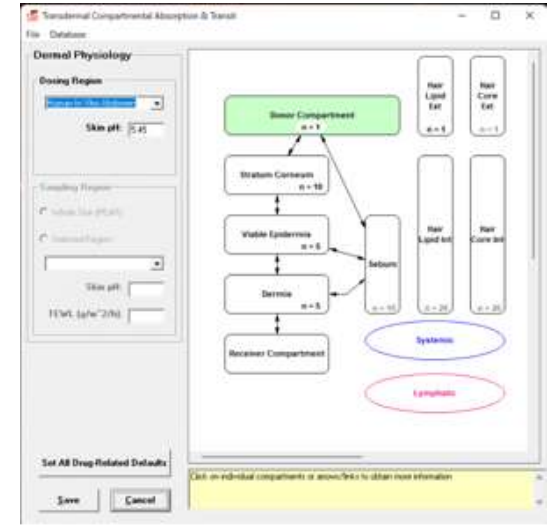
$P$  : Air pressure

$L$  : Characteristic length of evaporation

# GastroPlus® Dermal model (TCAT)

**入カパラメーター**  
 SMILES記法による分子構造式  
 分子量  
 油水分配係数  
 適用濃度  
 適用容量  
 飽和溶解度  
 適用時間

**入カパラメーター：基剤の揮発速度**  
 $K_{ved}$ : 固定値



S. Grégoire, et al., *Computational Toxicology*, **19**, 2021

# 化学物質のヒト皮膚透過パラメータの予測

ヒト皮膚の皮膚透過パラメータ（角層中および生きた表皮・真皮中への物質の分配係数（ $K$ ）および拡散係数（ $D$ ））の実測値  
CA. Ellison *et al.*, *Toxicology in Vitro*, **69**, 104990-105050 (2020)より引用

Toxicology in Vitro 69 (2020) 104990



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Toxicology in Vitro

journal homepage: [www.elsevier.com/locate/toxinvit](http://www.elsevier.com/locate/toxinvit)



## Partition coefficient and diffusion coefficient determinations of 50 compounds in human intact skin, isolated skin layers and isolated stratum corneum lipids



Corie A. Ellison<sup>a,\*</sup>, Kevin O. Tankersley<sup>a</sup>, Cindy M. Obringer<sup>a</sup>, Greg J. Carr<sup>a</sup>, John Manwaring<sup>a,1</sup>, Helga Rothe<sup>b,2</sup>, H el ene Duplan<sup>c</sup>, Camille G eni es<sup>c</sup>, S ebastien Gr egoire<sup>d</sup>, Nicola J. Hewitt<sup>e</sup>, Carine Jacques Jamin<sup>c</sup>, Martina Klaric<sup>e,3</sup>, Daniela Lange<sup>f</sup>, Alexandra Rolaki<sup>e</sup>, Andreas Schepky<sup>f</sup>

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<sup>b</sup> Procter and Gamble, Darmstadt, Germany

<sup>c</sup> Pierre Fabre Dermo-Cosm etique, Toulouse, France

<sup>d</sup> L'Oreal Research and Innovation, Aulnay-Sous-Bois, France

<sup>e</sup> ADME Task Force, Cosmetics Europe, Brussels, Belgium

<sup>f</sup> Beiersdorf AG, Hamburg, Germany

### ARTICLE INFO

#### Keywords:

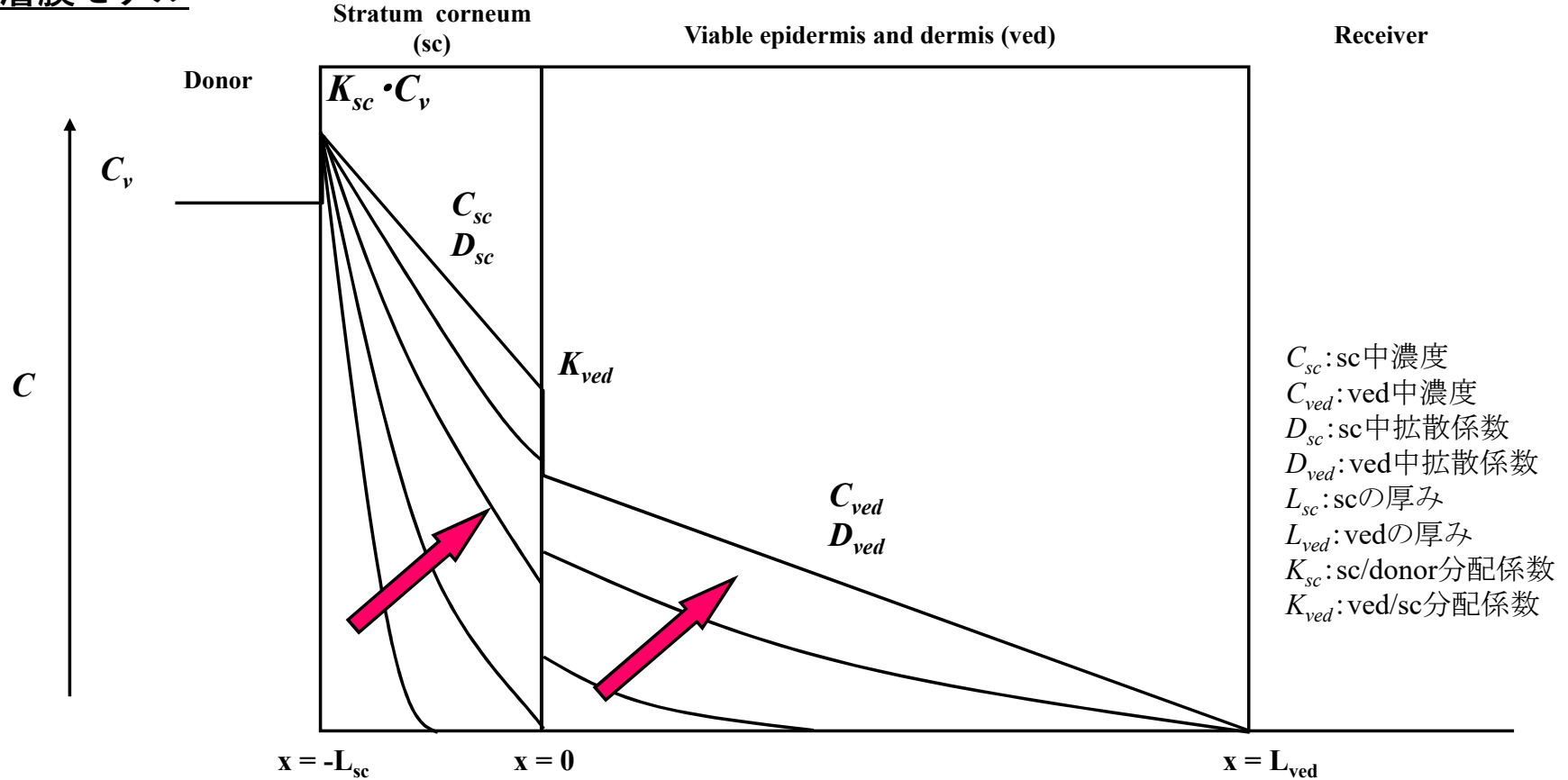
Skin absorption  
Skin penetration  
Partition coefficient  
Diffusion coefficient  
Infinite dose

### ABSTRACT

A standard protocol was used to determine partition ( $K$ ) and diffusion ( $D$ ) coefficients in dermatomed human skin and isolated human skin layers for 50 compounds relevant to cosmetics ingredients.  $K$  values were measured in dermatomed skin, isolated dermis, whole epidermis, intact stratum corneum (SC), delipidized SC and SC lipids by direct measurements of the radioactivity in the tissue layers/lipid component vs. buffer samples.  $D$  determinations were made in dermatomed skin, isolated dermis, whole epidermis and intact SC using a non-linear regression of the cumulative receptor fluid content of radiolabeled compound, fit to the solution of Fick's 2nd Law. Correlation analysis was completed between  $K$ ,  $D$ , and physicochemical properties. The amount of inter-individual (donor) and intraindividual (replicate) variability in the  $K$  and  $D$  data was characterized for each skin layer and chemical. These data can be further used to help inform the factors that influence skin bioavailability and to help improve in silico models of dermal penetration.

# 皮膚中濃度－皮膚深度プロファイル (無限用量系)

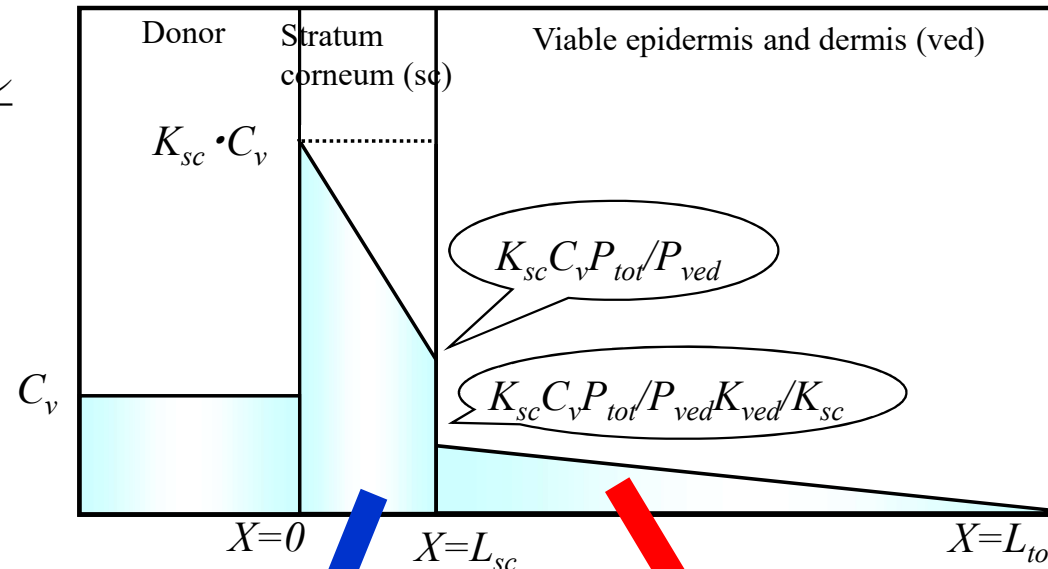
## 皮膚2層膜モデル





# 皮膚透過パラメータを用いた皮膚中濃度予測（無限用量系）

皮膚2層膜モデル



- $C_{sc}$ : sc中濃度
- $C_{ved}$ : ved中濃度
- $D_{sc}$ : sc中拡散係数
- $D_{ved}$ : ved中拡散係数
- $L_{sc}$ : scの厚み
- $L_{ved}$ : vedの厚み
- $K_{sc}$ : sc/donor分配係数
- $K_{ved}$ : ved/sc分配係数

Concentration in stratum corneum

$$\bar{C}_{ss,sc} = \frac{K_{sc} \cdot C_v + K_{sc} \cdot C_v \cdot P_{tot} / P_{ved}}{2}$$

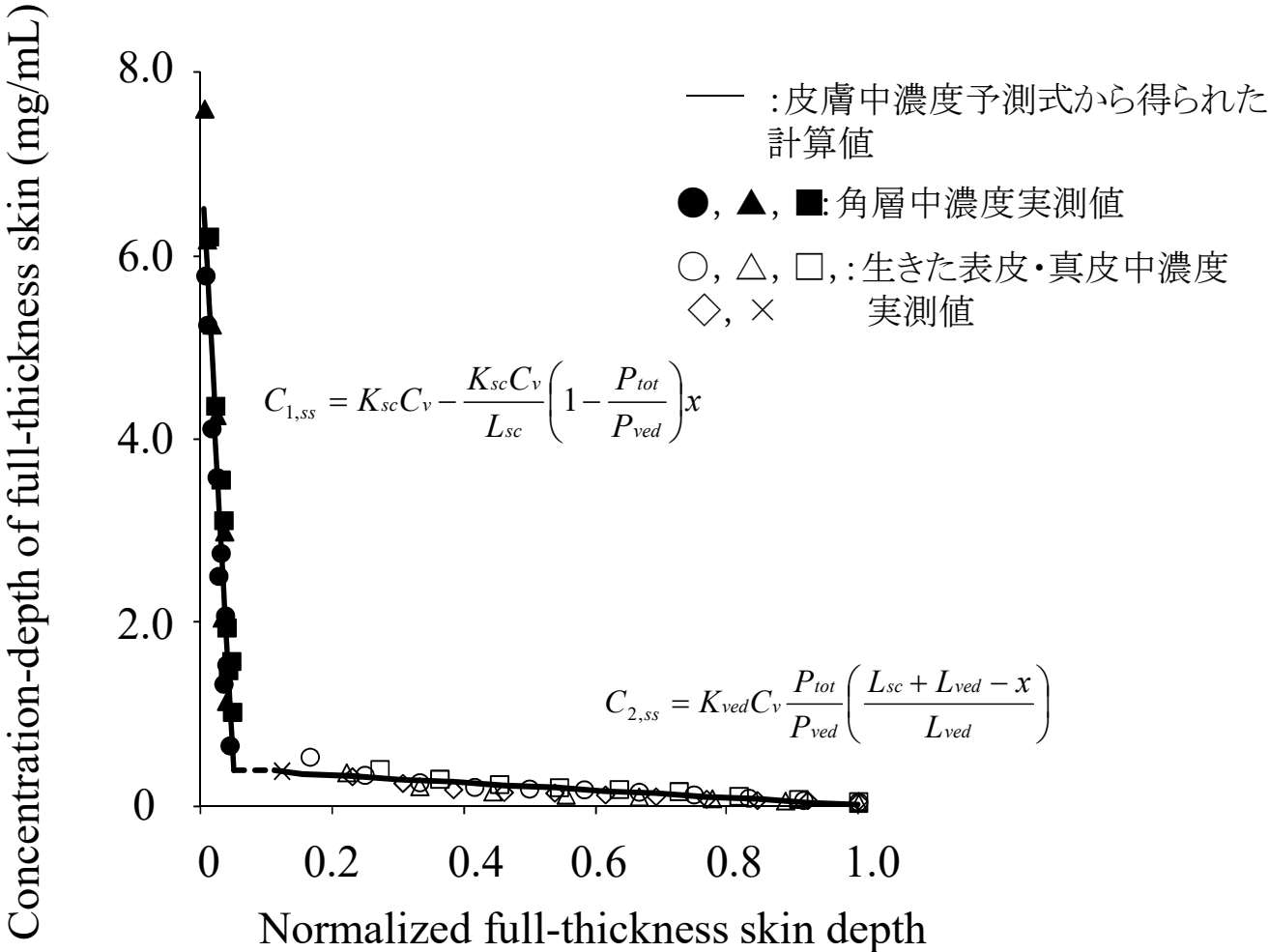
Concentration in viable epidermis and dermis

$$\bar{C}_{ss,ved} = \frac{K_{ved} \cdot C_v \cdot P_{tot} / P_{ved}}{2}$$

Total concentration in skin

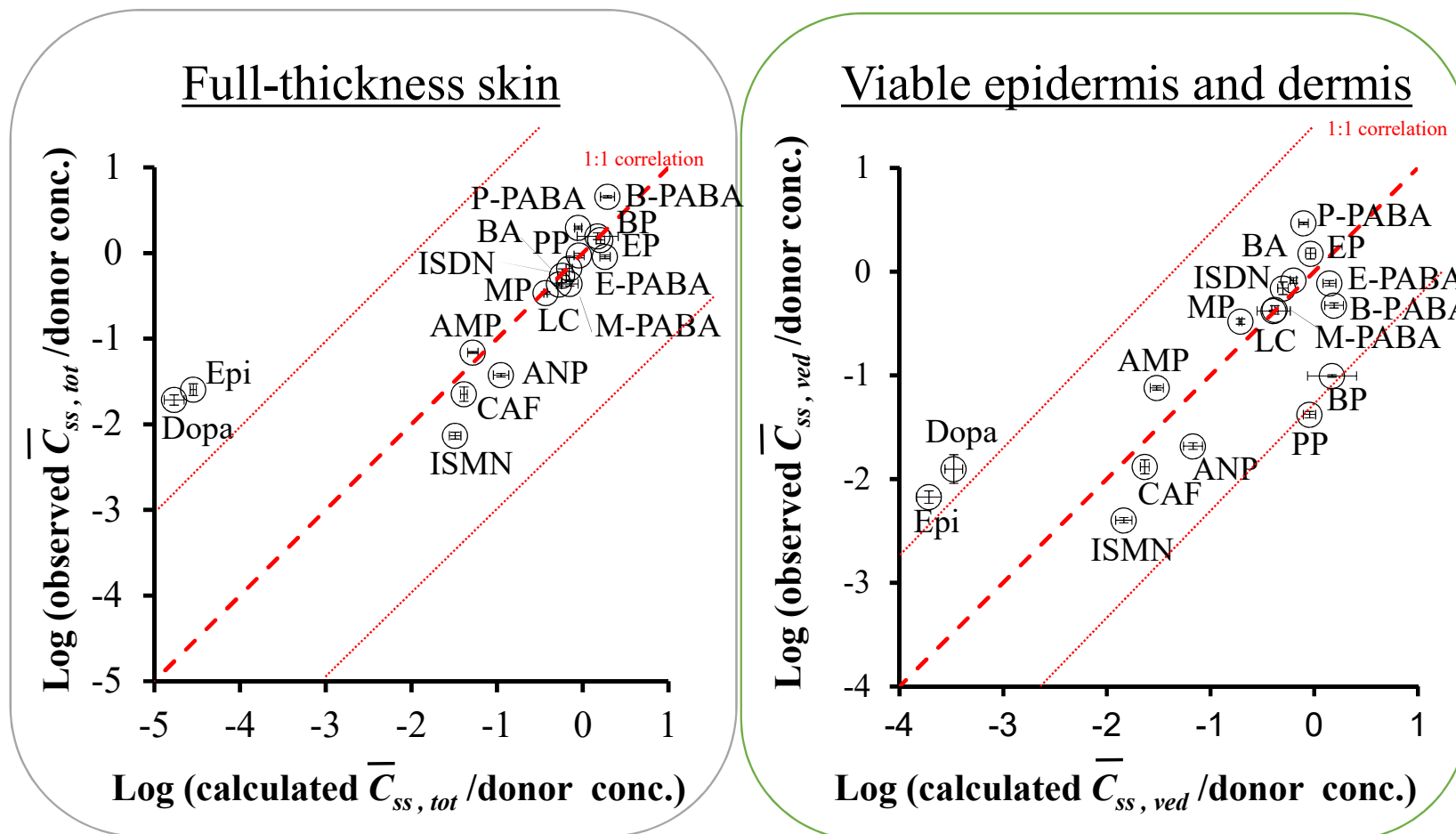
$$\bar{C}_{ss} = \frac{C_v}{2 \cdot L_{tot}} \left\{ K_{sc} \cdot L_{sc} \cdot (1 + P_{tot} / P_{ved}) + K_{ved} \cdot L_{ved} \cdot P_{tot} / P_{ved} \right\}$$

# 皮膚透過性と皮膚中濃度式:各深度の皮膚中濃度



Oshizaka T., Todo H., Hatanaka T., Sugibayashi K., *Int. J. Pharm.*, **475**, 292-297 (2014)

# 皮膚透過パラメータを用いた皮膚中濃度予測



Data range:  $122.12 < M.W. < 234.30$ ,  $-5.54 < ClogP < 3.57$

Mean  $\pm$  S.E. (n = 4)



## 物理化学的特性値の算出

M.W.  
logP  
LUMO.eV  
HOMO.eV  
HOMO.LUMO.GAP  
融点  
双極子モーメント  
生成熱  
電子親和力  
イオン化エネルギー  
Absolute hardness  
chemical potential  
H.bond.donors  
H.bond.acceptors

Compound	M.W.	logP	Compound	M.W.	logP
2,4'-Dichloroacetophenone	189.0	2.7	Cinnamyl alcohol	134.2	2.0
2,4-Dinitrochlorobenzene	202.5	2.2	Dimethyl phthalate	194.2	1.6
2-Acetylaminofluorene	223.3	3.3	Ethylumbelliferone	190.2	2.3
2-Ethylhexyl acrylate	184.3	3.8	Eugenol	164.2	2
3-Methyl-3H-imidazo[4,5-f]quinolin-2-amine	198.2	1.5	Geraniol	154.3	2.9
4-Bromophenyl Isocyanate	198.0	3.4	Hydrocortisone	362.5	1.6
4-Chloroaniline	127.6	1.9	Ibuprofen	206.3	4.0
4-Methylpentanoic acid	116.7	1.4	Isoeugenol	164.2	2.6
6-Methylcoumarin	160.2	1.8	Naphthalene	128.2	3.3
Benzoic acid	122.1	1.9	propyl 4-aminobenzoate	179.2	2.4
Benzophenone	182.2	3.4	p-Tolunitrile	117.2	2.4
Benzyl bromide	171.0	2.9	propylparaben	180.2	3
Benzylideneacetone	146.2	2.1	Salicylic acid	138.1	2.3
Cinnamaldehyde	132.2	1.9	Testosterone	288.4	3.3
Cinnamic acid	148.2	2.1	Tetramethyl thiuram disulfide	240.4	1.7
			Vanillin	152.2	1.1

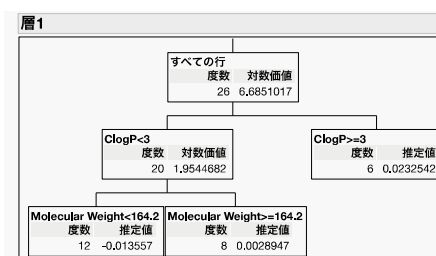
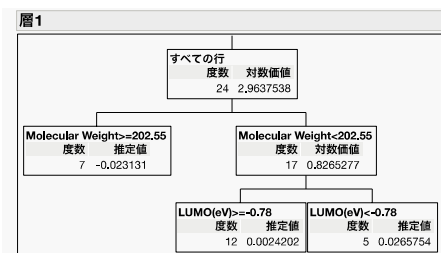
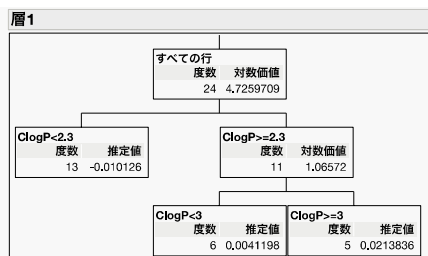
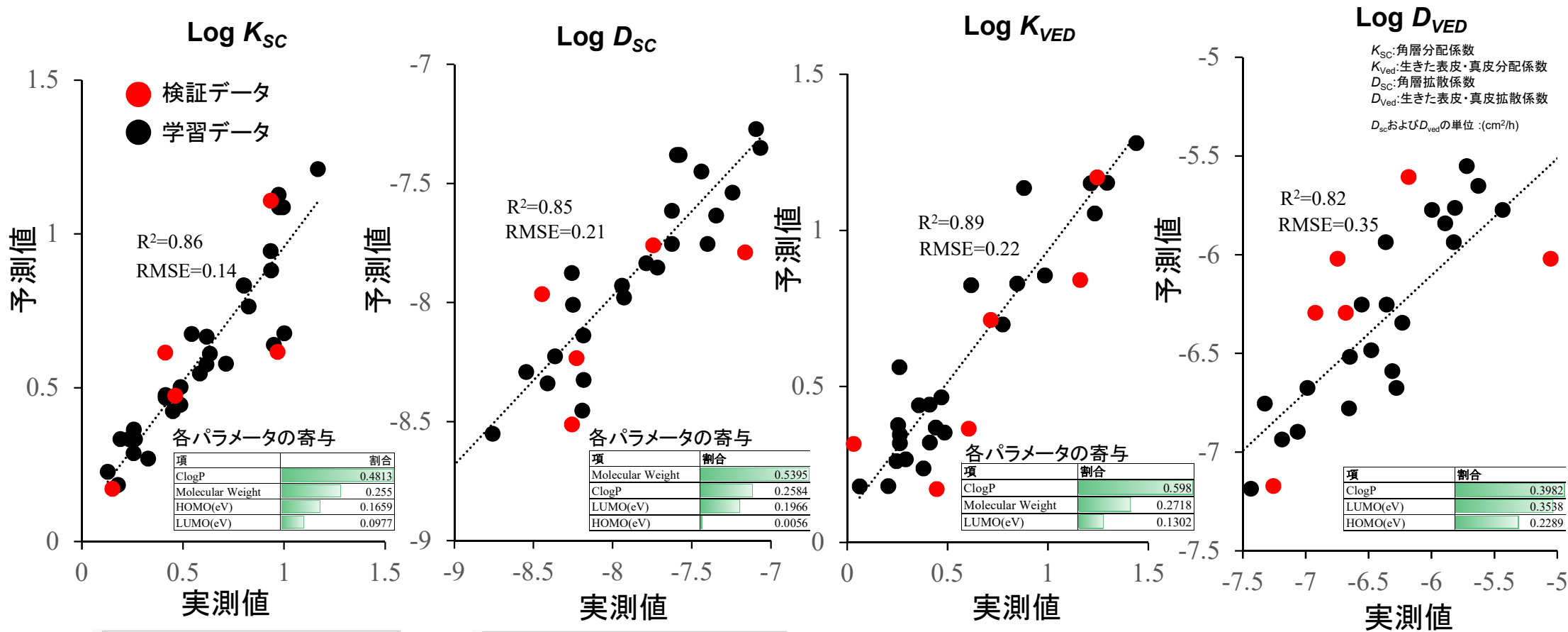
JMP proによる解析 非線形回帰モデル 機械的学習法 勾配ブーストストラップ

分子量、ClogP、LUMO、HOMOから  
皮膚透過パラメータを予測



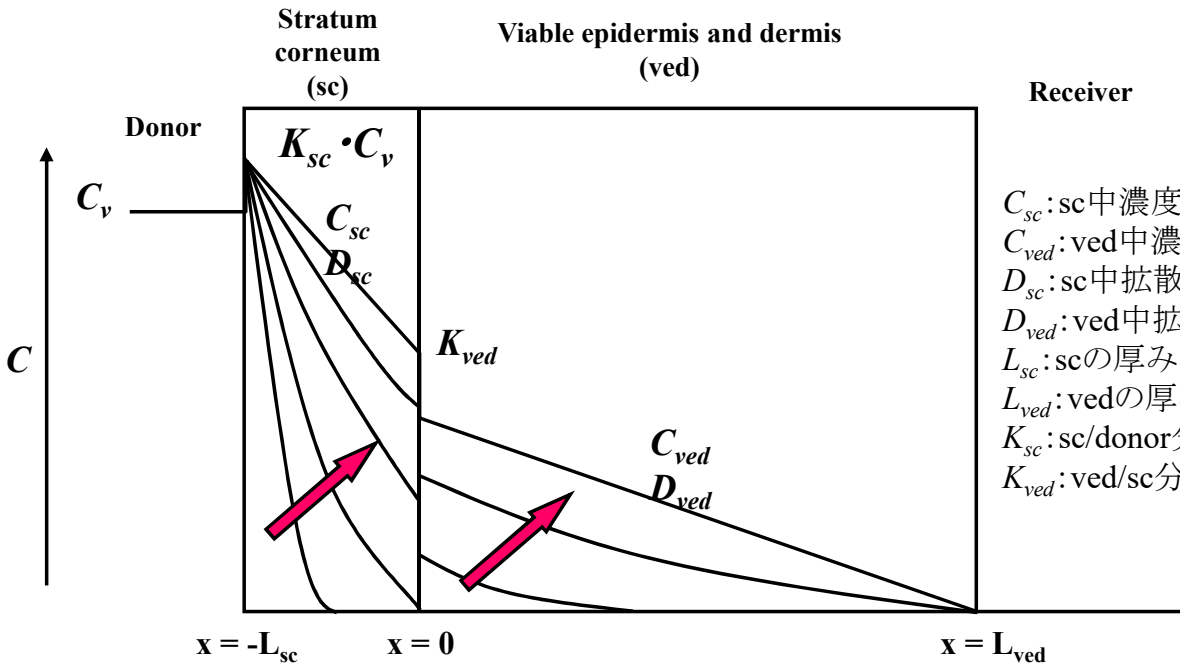


# 皮膚透過パラメーターの予測値と実測値の相関



# 皮膚中濃度ー皮膚深度プロファイル (無限用量系)

皮膚2層膜モデル



- $C_{sc}$ : sc中濃度
- $C_{ved}$ : ved中濃度
- $D_{sc}$ : sc中拡散係数
- $D_{ved}$ : ved中拡散係数
- $L_{sc}$ : scの厚み
- $L_{ved}$ : vedの厚み
- $K_{sc}$ : sc/donor分配係数
- $K_{ved}$ : ved/sc分配係数

$$\frac{\partial C_{sc}}{\partial t} = D_{sc} \frac{\partial^2 C_{sc}}{\partial x^2}$$

$$\frac{\partial C_{ved}}{\partial t} = D_{ved} \frac{\partial^2 C_{ved}}{\partial x^2}$$

$$t=0 \quad -L_{sc} < x < 0 \quad C_{sc} = 0$$

$$0 < x < L_{ved} \quad C_{ved} = 0$$

$$t>0 \quad x = -L_{sc} \quad C_{sc} = K_{sc} \cdot C_v$$

$$x = 0 \quad C_{ved} = K_{ved} \cdot C_{sc} \text{ and } D_{sc} \frac{dC_{sc}}{dx} = D_{ved} \frac{dC_{ved}}{dx}$$

$$x = 0 \quad C_{ved} = 0$$

$$Q = -D_{ved} \int_0^t \left( \frac{dC_{ved}}{dx} \right)_{x=L_{ved}} dt$$

$$\frac{dC_{i,j}}{dt} = \frac{1}{\Delta t} (C_{i,j+1} - C_{i,j})$$

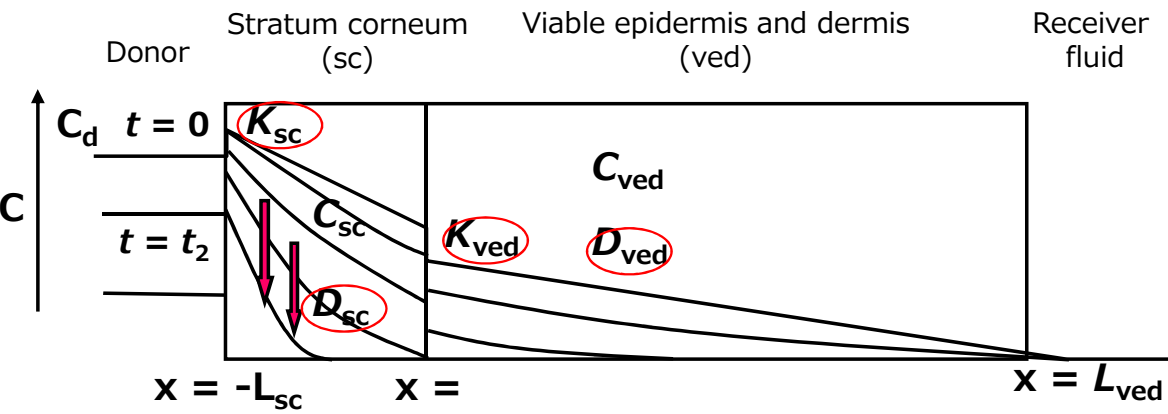
$$\frac{d^2 C_{i,j}}{dx^2} = \frac{1}{\Delta x^2} (C_{i-1,j} - 2C_{i,j} + C_{i+1,j})$$

$$C_{sc}(t) = K_{sc} \cdot C_v(t)$$

化学物質を有限用量系で適用したときの皮膚吸収量予測を可能とするモデルの構築

有限用量系  
二層膜モデル  
皮膚透過パラメータ

適用製剤容量  
適用製剤濃度



皮膚の厚み (角層、生きた表皮・真皮)

角層

生きた表皮・真皮

累積皮膚透過量

適用時間

角層中の各深度での物質濃度

生きた表皮・真皮中の各深度での物質濃度

Layer model	FINITE	Stratum corneum	Viable epidermis and dermis	Receiver fluid
D (cm <sup>2</sup> /s)	7.8E-07	0.00442118	0.00011000	0.00011000
K (sc:donor)	2.7396	6.9995E-01	1.0000E+00	1.0000E+00
K (ved:sc)	0.818556	0.1499E+00	1.0000E+00	1.0000E+00
K (ved:fluid)	0.951261	0.0000E+00	1.0000E+00	1.0000E+00
D (ved)	0.00033333	0.00033333	0.00033333	0.00033333
Vol (cm <sup>3</sup> )	0.01	0.00011000	0.00011000	0.00011000
A (cm <sup>2</sup> )	1	1	1	1
evaporation rate (g/h)	0.0252			
Volume	Conc.			
0.01	0.00011000			
0.00099418	577.2474316	0.00033333	0.00033333	0.00033333
0.00099748	577.5051229	0.00046467	0.00046467	0.00046467
0.000997986	578.2706444	0.00059601	0.00059601	0.00059601
0.000998176	579.0351567	0.00072735	0.00072735	0.00072735
0.00099824	579.8000094	0.00085869	0.00085869	0.00085869
0.000999236	579.5644708	0.00099003	0.00099003	0.00099003
0.000999448	579.3289322	0.00112137	0.00112137	0.00112137
0.000999277	579.0933936	0.00125271	0.00125271	0.00125271
0.000999172	578.8578550	0.00138405	0.00138405	0.00138405
0.000999382	578.6223164	0.00151539	0.00151539	0.00151539
0.000998959	578.3867778	0.00164673	0.00164673	0.00164673
0.000999148	578.1512392	0.00177807	0.00177807	0.00177807
0.000999453	577.9157006	0.00190941	0.00190941	0.00190941
0.000999333	577.6801620	0.00204075	0.00204075	0.00204075
0.000998488	577.4446234	0.00217209	0.00217209	0.00217209
0.000998243	577.2090848	0.00230343	0.00230343	0.00230343
0.000998581	576.9735462	0.00243477	0.00243477	0.00243477
0.000999681	576.7380076	0.00256611	0.00256611	0.00256611
0.000999834	576.5024690	0.00269745	0.00269745	0.00269745
0.000999939	576.2669304	0.00282879	0.00282879	0.00282879
0.000999994	576.0313918	0.00296013	0.00296013	0.00296013
0.000999999	575.7958532	0.00309147	0.00309147	0.00309147
0.000999999	575.5603146	0.00322281	0.00322281	0.00322281
0.000999999	575.3247760	0.00335415	0.00335415	0.00335415
0.000999999	575.0892374	0.00348549	0.00348549	0.00348549
0.000999999	574.8536988	0.00361683	0.00361683	0.00361683
0.000999999	574.6181602	0.00374817	0.00374817	0.00374817
0.000999999	574.3826216	0.00387951	0.00387951	0.00387951
0.000999999	574.1470830	0.00401085	0.00401085	0.00401085
0.000999999	573.9115444	0.00414219	0.00414219	0.00414219
0.000999999	573.6760058	0.00427353	0.00427353	0.00427353
0.000999999	573.4404672	0.00440487	0.00440487	0.00440487
0.000999999	573.2049286	0.00453621	0.00453621	0.00453621
0.000999999	572.9693900	0.00466755	0.00466755	0.00466755
0.000999999	572.7338514	0.00479889	0.00479889	0.00479889
0.000999999	572.4983128	0.00493023	0.00493023	0.00493023
0.000999999	572.2627742	0.00506157	0.00506157	0.00506157
0.000999999	572.0272356	0.00519291	0.00519291	0.00519291
0.000999999	571.7916970	0.00532425	0.00532425	0.00532425
0.000999999	571.5561584	0.00545559	0.00545559	0.00545559
0.000999999	571.3206198	0.00558693	0.00558693	0.00558693
0.000999999	571.0850812	0.00571827	0.00571827	0.00571827
0.000999999	570.8495426	0.00584961	0.00584961	0.00584961
0.000999999	570.6140040	0.00598095	0.00598095	0.00598095
0.000999999	570.3784654	0.00611229	0.00611229	0.00611229
0.000999999	570.1429268	0.00624363	0.00624363	0.00624363
0.000999999	570.0000000	0.00637497	0.00637497	0.00637497

蒸発速度算出: Kawamura and Mackay式

$$E = Ar \times K_M \times \{(M_W \times PV)/(R \times T)\}$$

E: 蒸発速度 (kg/s), Ar: 液面面積 (m<sup>2</sup>), K<sub>M</sub>: 物質移動係数 (m/s), M<sub>W</sub>: 分子量 (g/mol), P<sub>V</sub>: 蒸気圧 (Pa), R: 気体定数 (J/(kmol·K)), T: 気相の熱力学的温度 (K)

水の揮発に伴う適用物質の皮膚表面での濃度上昇  
水基剤中の飽和溶解度  
皮膚透過に伴う基剤中物質の減少  
水が完全に揮発すると皮膚表面への物質の分配停止

# In vitro 皮膚透過試験

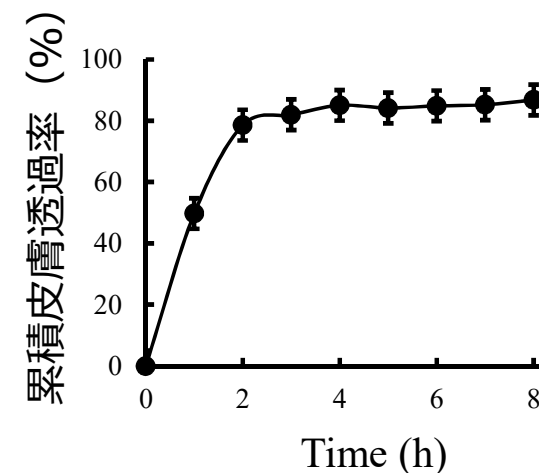
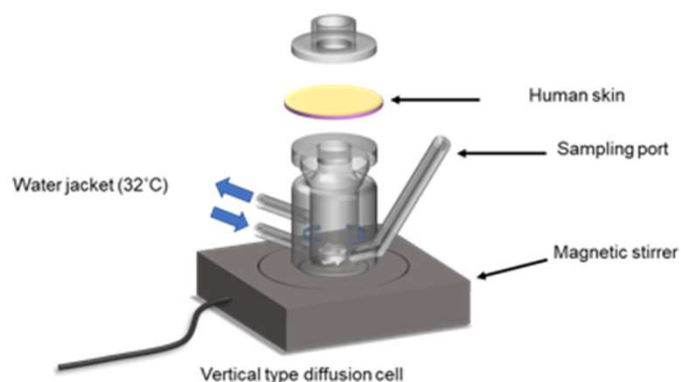
各試験物質の水への飽和溶解度の60%濃度で適用  
精製水を用いて適用製剤を調製

試験物質(10物質)

Chemical name	M.W.	*XLogP3
BR (4-Butylresorcinol)	166	2.4
ISDN (Isosorbide mononitrate)	236	1.3
MP (Methylparaben)	152	2.0
EP(Ethylparaben)	166	2.5
PP (propylparaben)	180	3.0
BP (Butylparaben)	194	3.6
M-PABA (Methyl p-aminobenzoate)	151	1.4
E-PABA (Ethyl p-aminobenzoate)	165	1.9
P-PABA (Propyl p-aminobenzoate)	179	2.4
B-PABA (Butyl p-aminobenzoate)	193	2.9

Membrane	Excised Human skin (Biopredic Internationalより購入)
Receiver	PBS (-)
Permeation area	1.77 cm <sup>2</sup>
Temperature	32°C
Application period	8 h
Application volume	<b>10 μL/cm<sup>2</sup></b>
Hydration time	1 h

有限用量系にて実施



\*PubChemより

## 改良前

E-PABA

累積透過量に大きな乖離がある。

## 改良点1

蒸発速度算出：Kawamura and Mackay式

$$E = Ar \times K_M \times \{(M_W \times PV)/(R \times T)\}$$

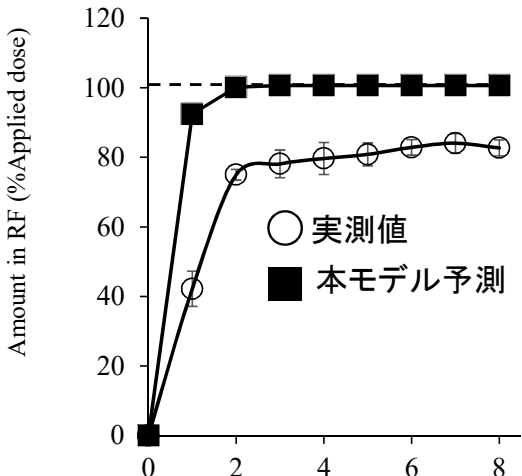
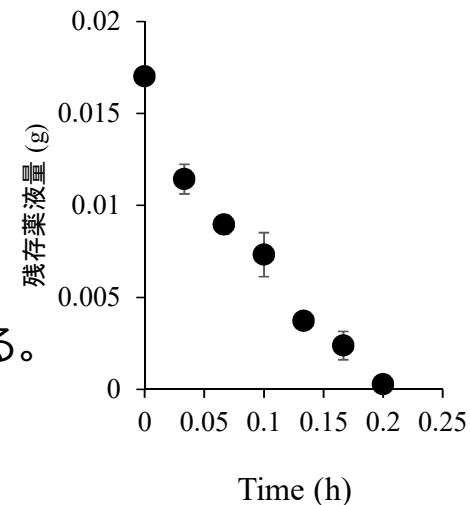
$E$ ：蒸発速度 (kg/s)、 $Ar$ ：液面面積 (m<sup>2</sup>)、 $K_M$ ：物質移動係数 (m/s)、 $M_W$ ：分子量 (g/mol)、 $P_V$ ：蒸気圧 (Pa)、 $R$ ：気体定数 (J/(kmol・K))、 $T$ ：気相の熱力学的温度 (K)

10 μL/cm<sup>2</sup>を適用しすると、約5分で蒸発する計算となる。

Gastroplusでは、約3分で蒸発する。

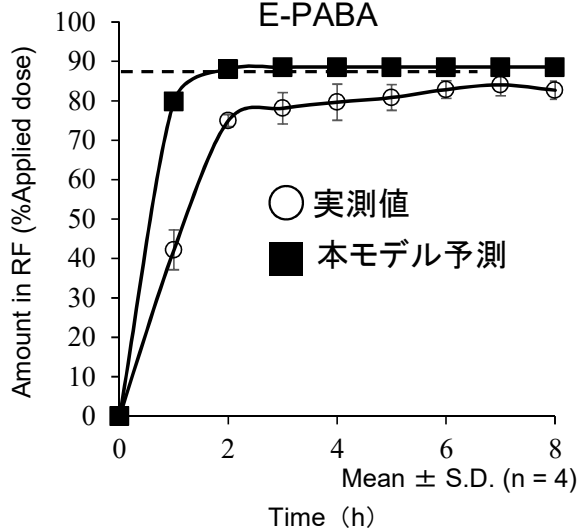
## 改良点2

透過面積：皮膚全体に広がらない



## 改良後

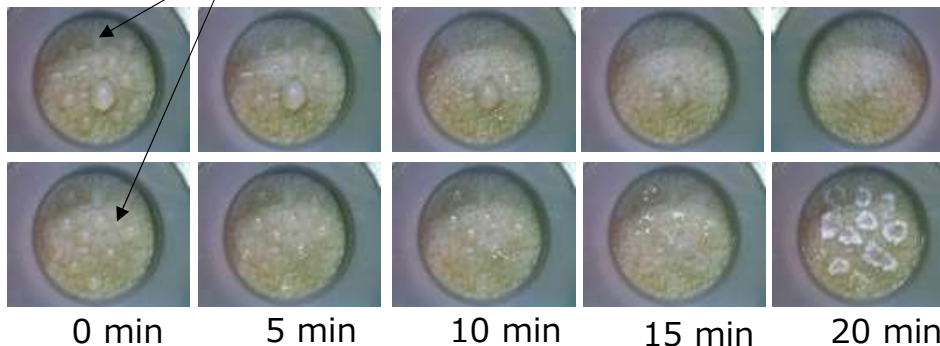
E-PABA



ヒト摘出皮膚

E-PABA  
水溶液適用  
10 μL/cm<sup>2</sup>

Caffein  
水溶液適用  
10 μL/cm<sup>2</sup>

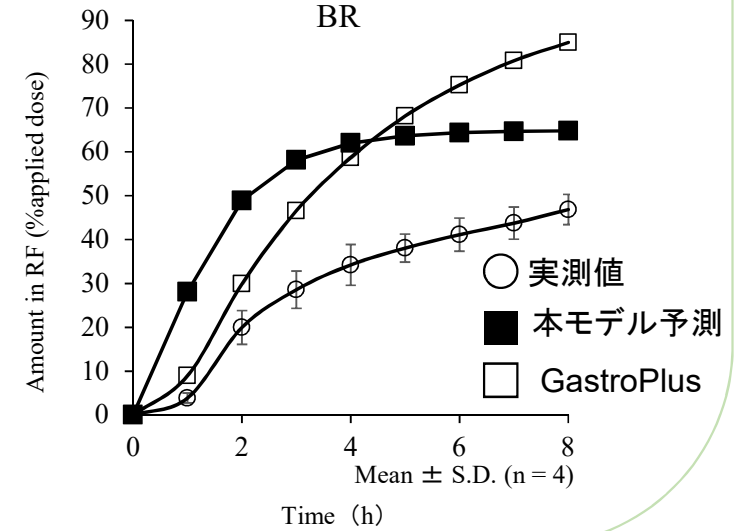
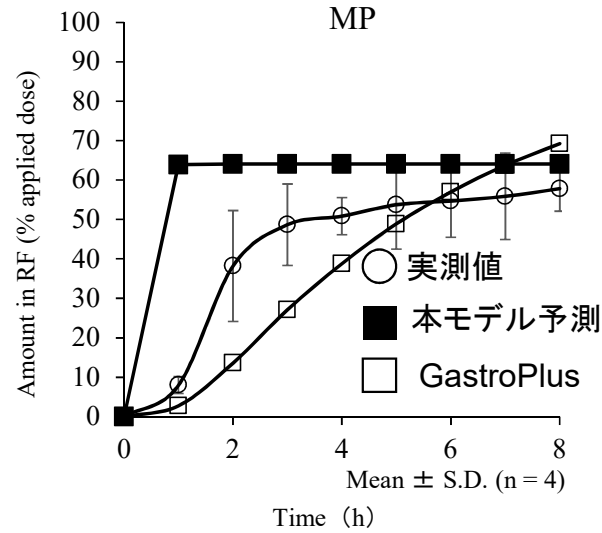
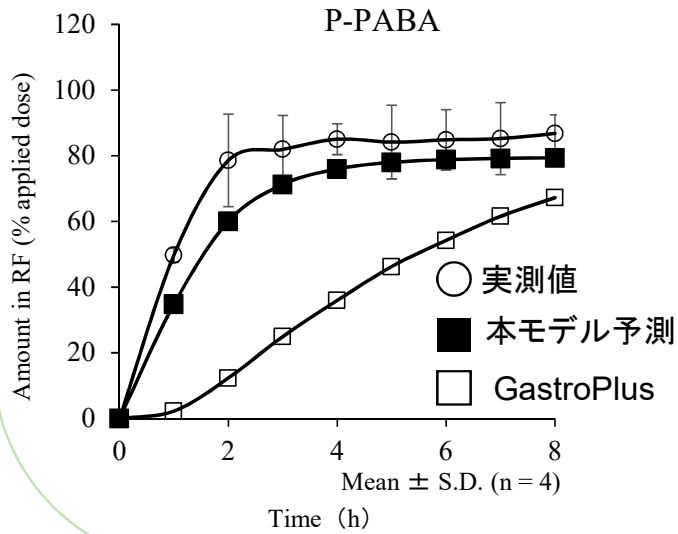
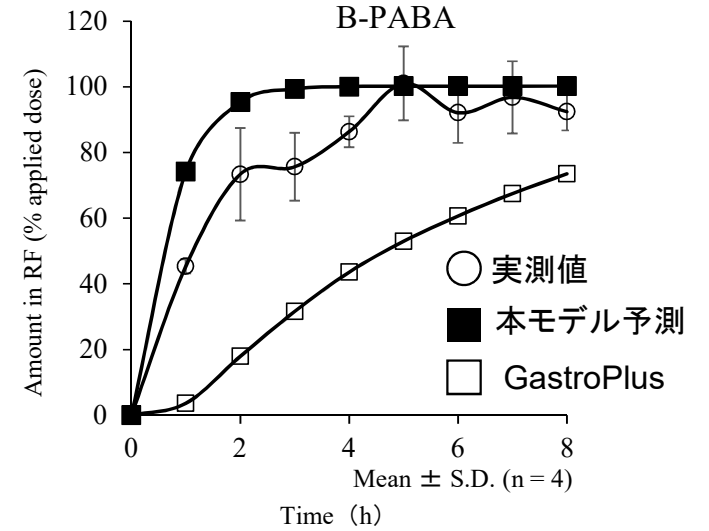
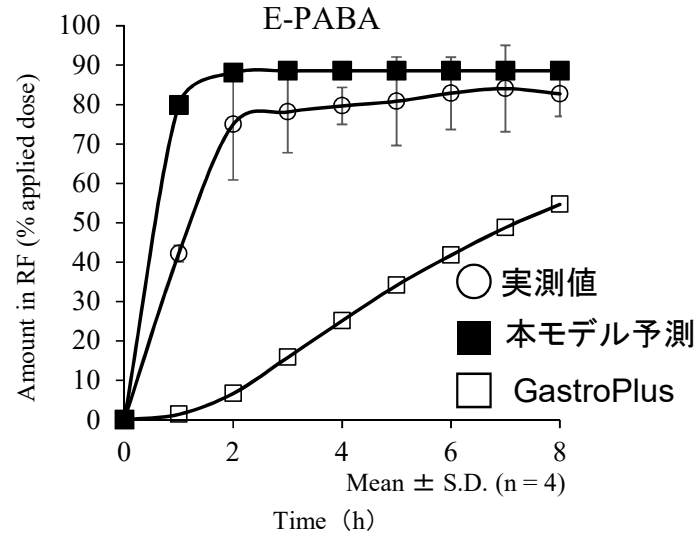
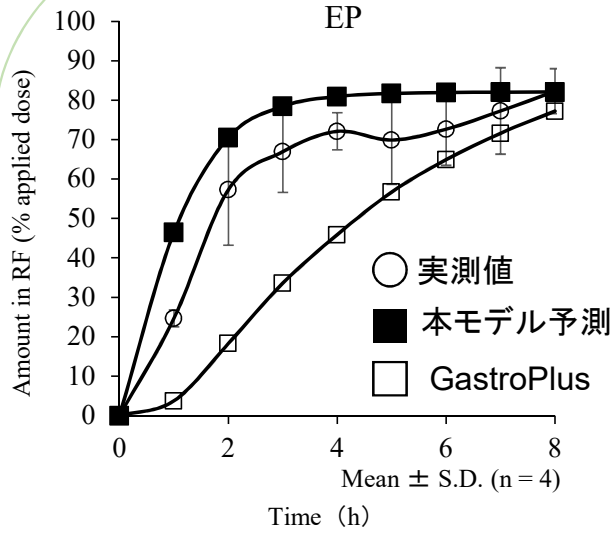


USB MICROSCOPE UM12  
(MicroLinks Technology Corp.)

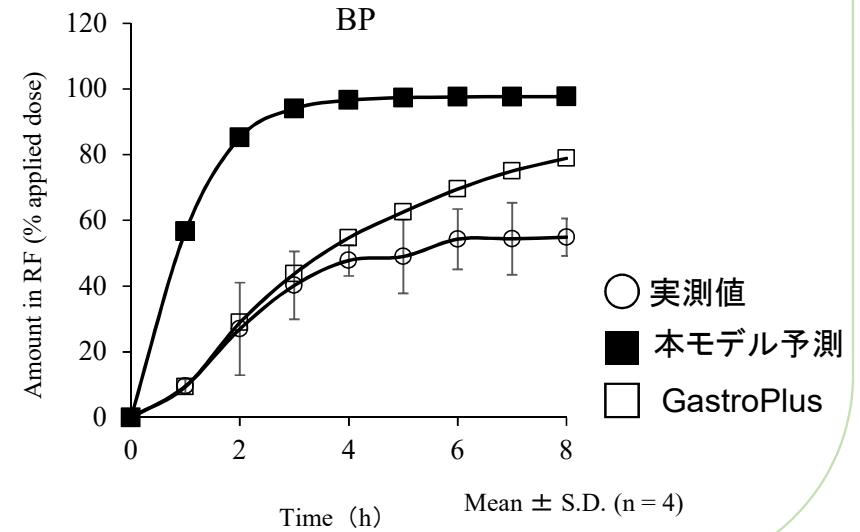
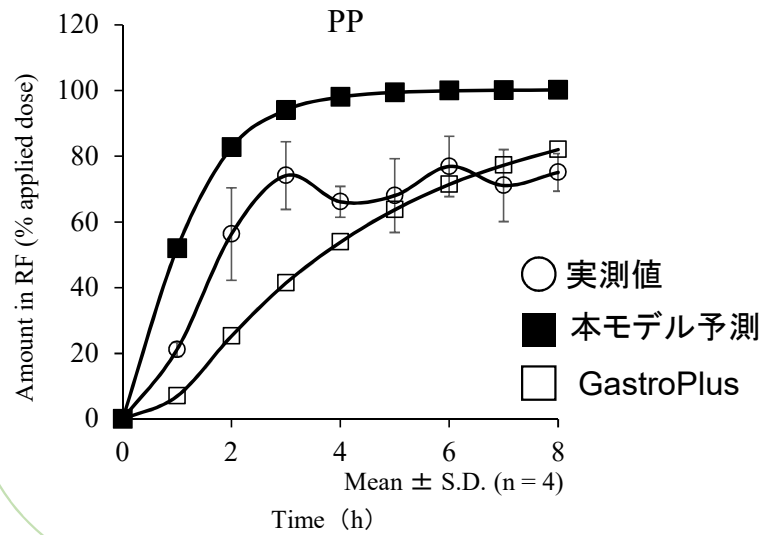
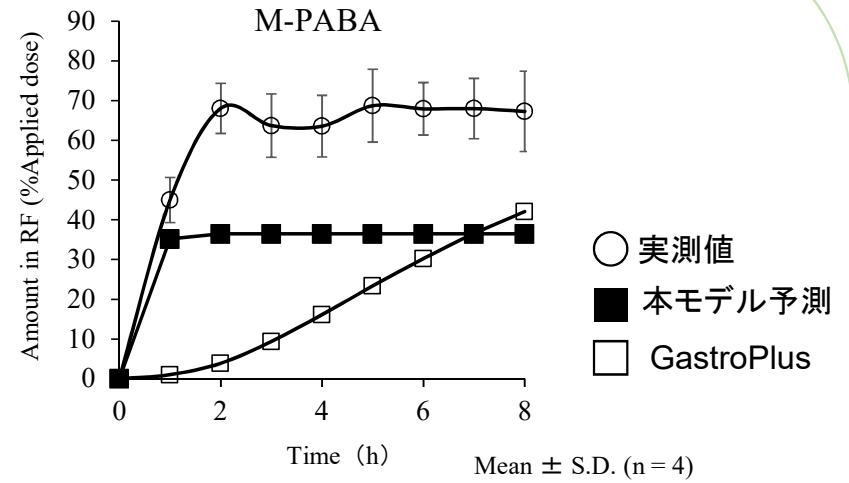
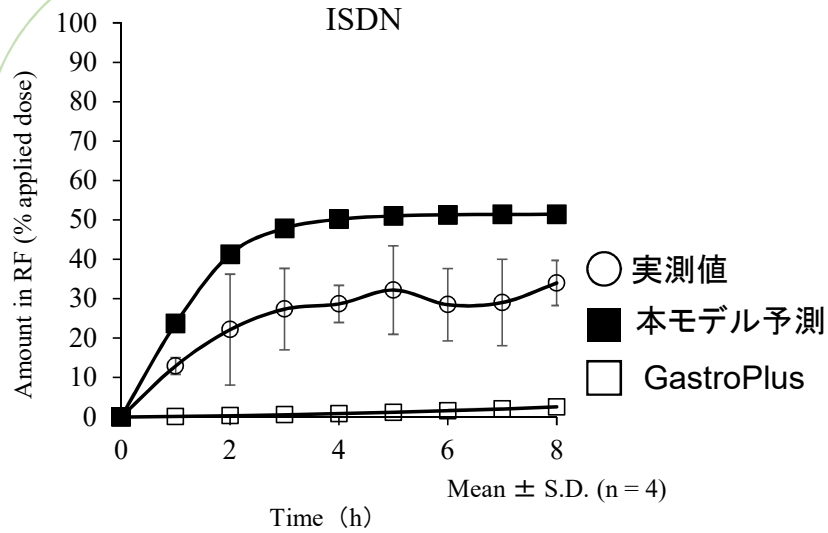
ImageJにて適用面積を算出



# 皮膚透過率の経時変化

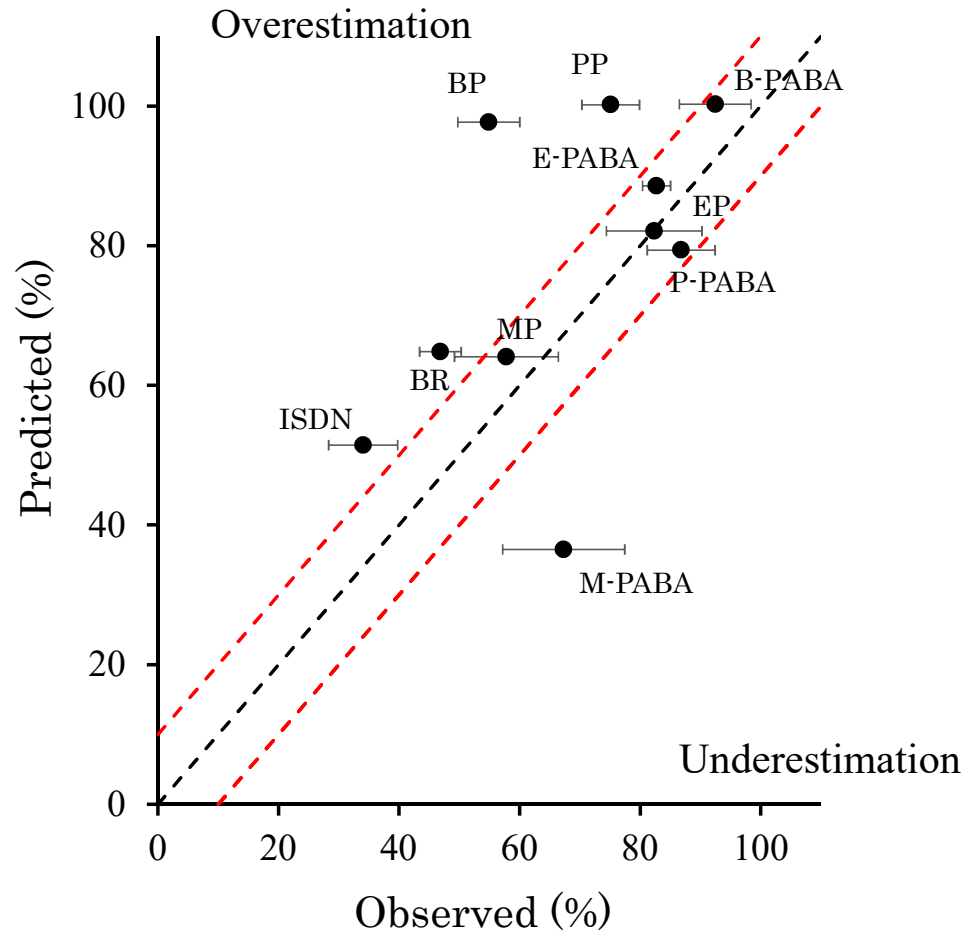


# 皮膚透過率の経時変化

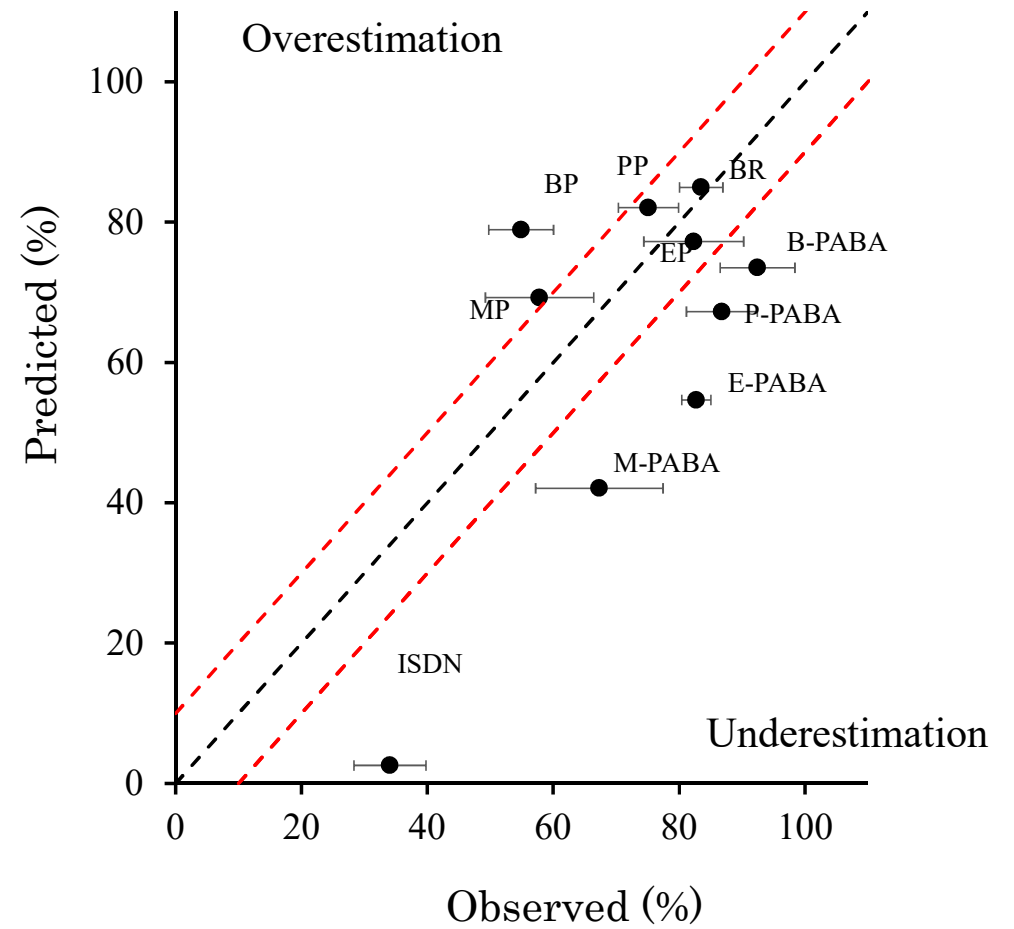


# 適用8時間後の皮膚透過率の実測値と予測値の相関

本モデル予測



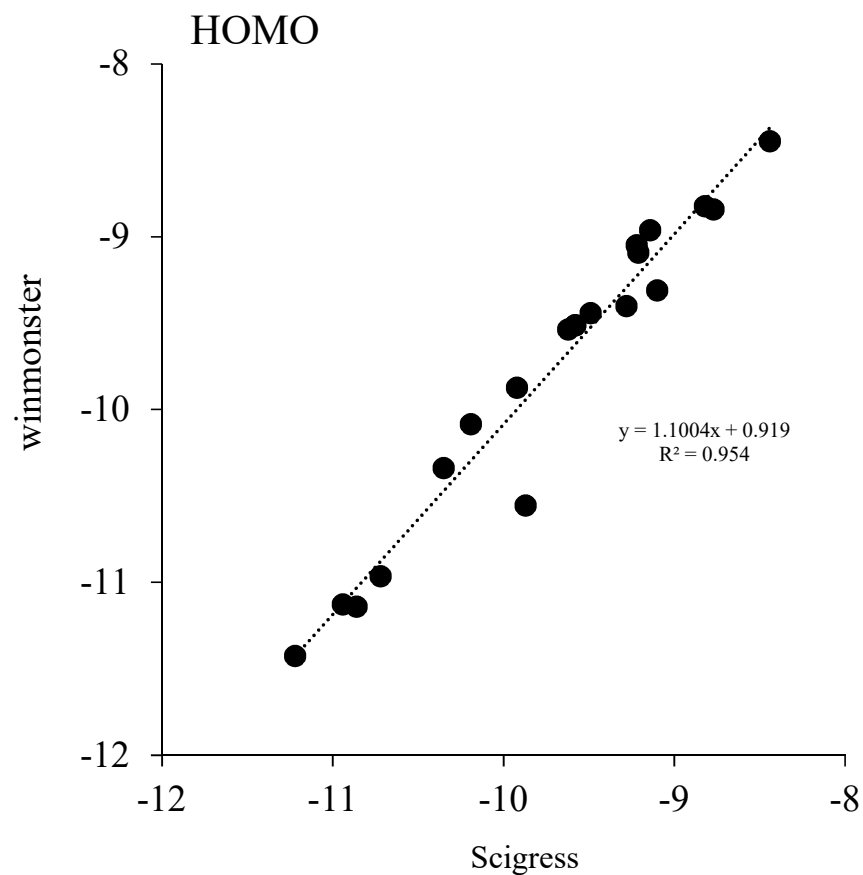
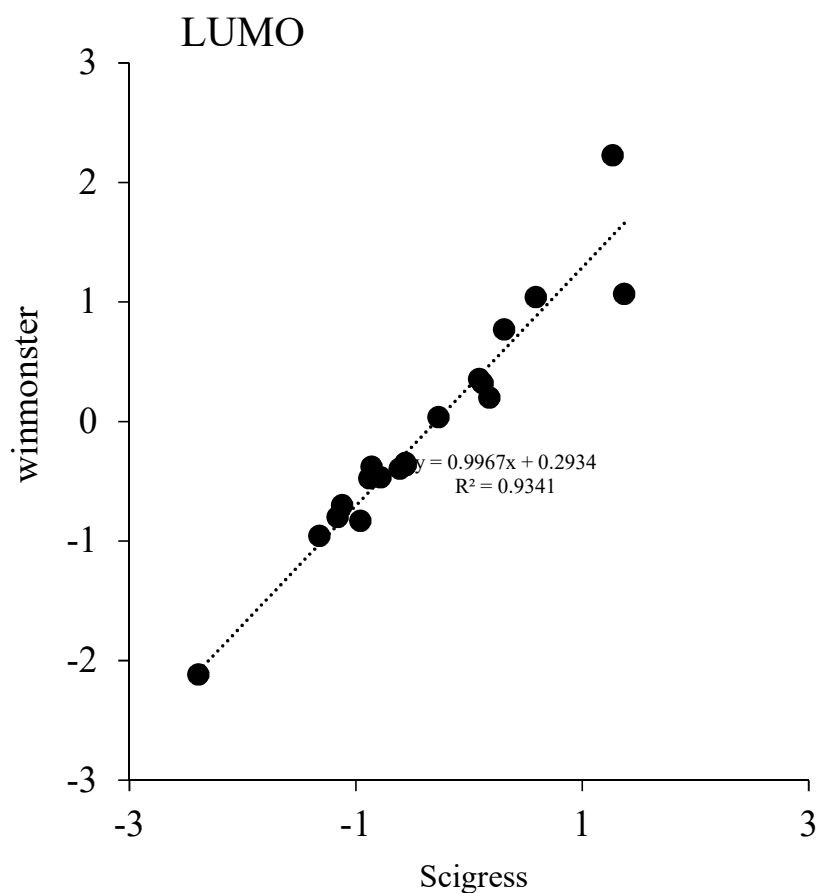
Gastroplus



# 有限用量系二層膜モデルの一般公開に向けた物理化学的特性値の予測

LUMOおよびHOMO: 無料のソフトウェアであるwinmonsterとSCIGRESSの互換性を確認

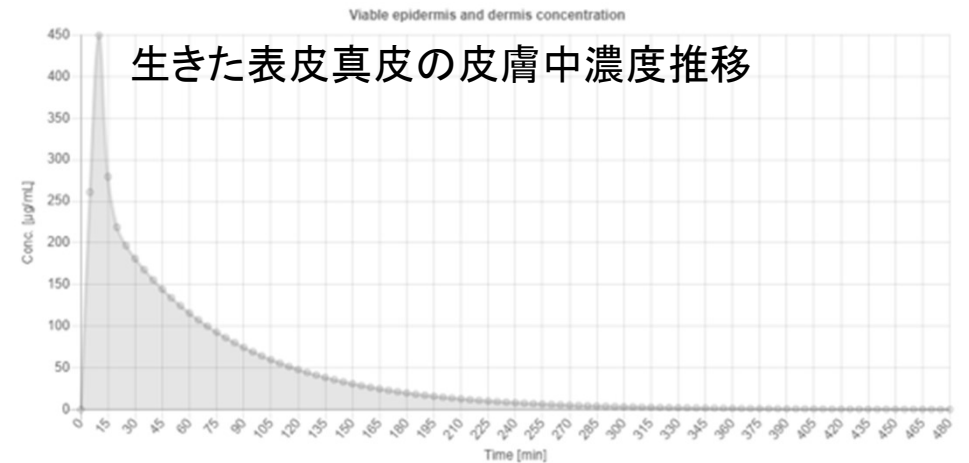
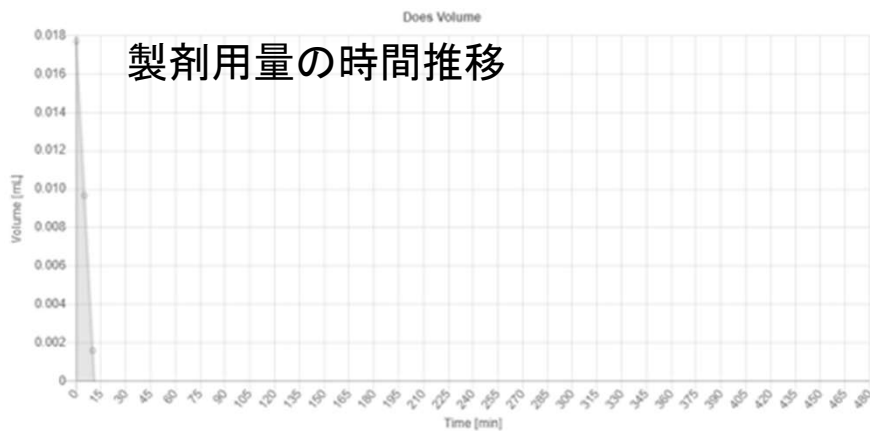
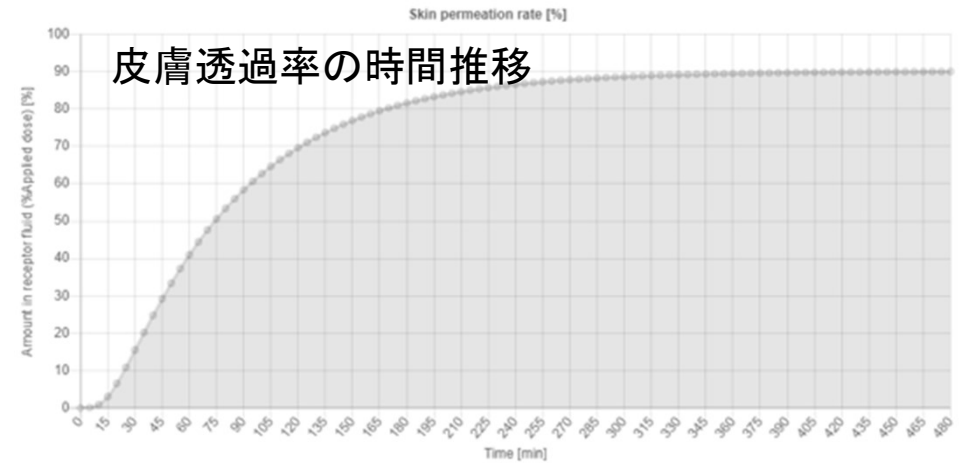
logP: PubChemのXlogP3



# Javascriptによる皮膚透過パラメータ予測および皮膚透過プロファイルシミュレーション

## 化学物質の皮膚暴露後の吸収挙動予測シミュレータ

M.W. API	<input type="text" value="179"/>		
XlogP3	<input type="text" value="2.43"/>		
LUMO(eV)	<input type="text" value="-0.19"/>		
HOMO(eV)	<input type="text" value="-8.77"/>		
Predict parameters			
logKsc	<input type="text" value="0.6455419363633336"/>	Ksc	<input type="text" value="4.421218070003292"/>
logDsc	<input type="text" value="-3.9479715653233347"/>	Dsc [cm/h]	<input type="text" value="0.00011272712598866345"/>
logKved	<input type="text" value="0.6421498209533335"/>	Kved	<input type="text" value="4.386820062163328"/>
logDved	<input type="text" value="-3.2576065524700017"/>	Dved [cm/h]	<input type="text" value="0.0005525778184831779"/>
L(sc) [cm]	<input type="text" value="0.002"/>	Cd [μg/mL]	<input type="text" value="300.405900719428"/>
L(ved) [cm]	<input type="text" value="0.0455"/>	Satu.Conc. [μg/mL]	<input type="text" value="526"/>
dt [h]	<input type="text" value="0.00033"/>	Km	<input type="text" value="1.36129032258065E-08"/>
Vd [mL]	<input type="text" value="0.0177"/>	Application time [h]	<input type="text" value="8"/>
A [cm^2]	<input type="text" value="0.584"/>	M.W. vehicle	<input type="text" value="18"/>
<input type="button" value="Calculate"/>			





# 謝辞

本研究は、日本化学工業協会が推進する LRI(Long-range Research Initiative;化学物質の環境影響および安全性に関する長期自主研究)により支援されました。

多大なるご支援を賜り、厚く感謝申し上げます。