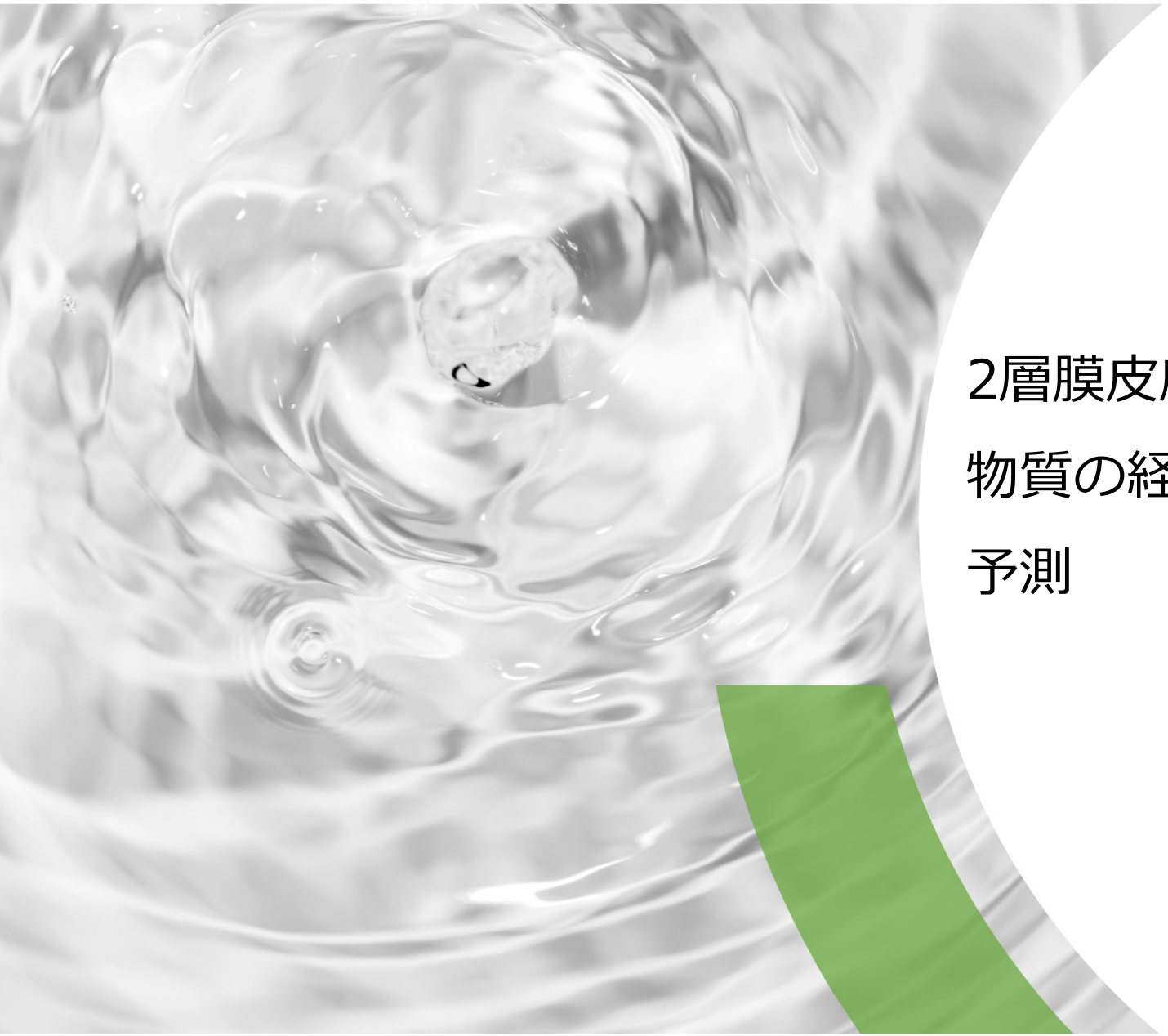
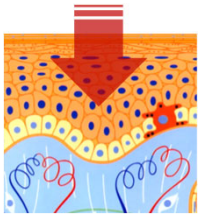


2層膜皮膚拡散モデルを用いた 化学物質の経皮暴露後の吸収性 *in silico* 予測

城西大学　薬学部
薬粧品動態制御学講座
藤堂　浩明

皮膚透過性および皮膚中濃度の把握

ハザード
薬(力価)
X
曝露量
=
リスク
効果

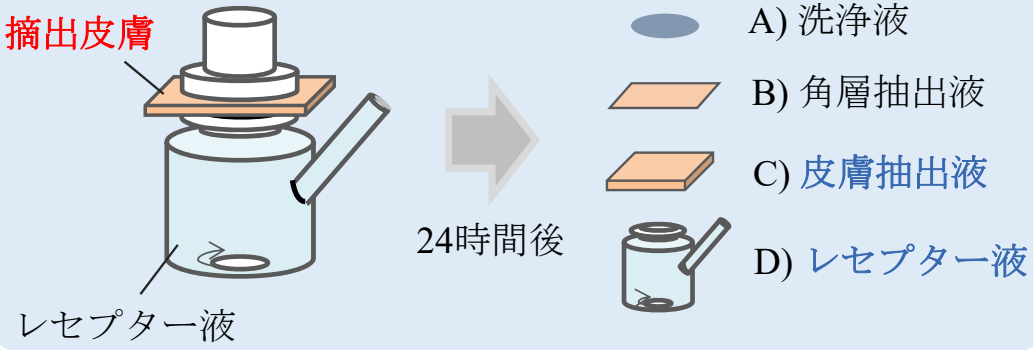


■ 曝露量と反応

安全性(リスク)と有効性(効果)の確認のため、ハザード物質や薬剤の曝露量の把握が重要
(化学物質の安全性評価；暴露量＝経皮吸収量)

経皮吸収量を測定するためには、
*in vitro*皮膚透過試験が必須

*In vitro*皮膚透過試験法 (OECD TG428)



経皮吸収量：C+Dの合計（角層より下に透過した量）

試験成立条件：A-Dの合計が塗布量の100±15%以内

摘出皮膚を用いた*in vitro*試験の課題

- 試験時間が長い（24時間+α）
- 高コスト
- 供給安定性
- 個体および部位差大

化学物質の皮膚透過性（透過係数：*P*）の予測

$$\log P\ (\mathrm{cm/s}) = 1.17\times10^{-7}K_{o/w}^{0.751}+2.73\times10^{-8}$$

Morimoto Y *et al.*, J Pharm Pharmcol., 44, 634-639 (1992)

$$\log P\ (\mathrm{cm/s}) = -6.3+0.71\times\log K_{o/w}-0.0061\times\mathrm{MW}$$

Potts RO, Guy RH, Pharm. Res., 9, 663-669 (1992)

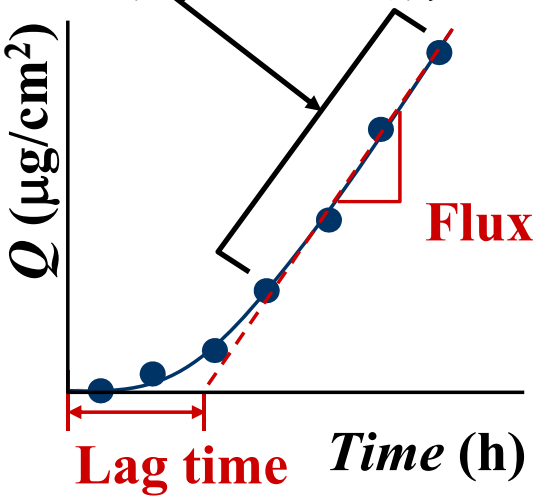
$$\log P\ (\mathrm{cm/s}) = -5.1+0.44R_2-0.49\pi_2^H -1.48\Sigma\alpha_2^H-3.44\ \Sigma\beta_2^H+1.94V_x$$

Abraham *et al.*, Pestic. Sci., 55, 78-88 (1999)

化合物の透過性の予測は数多く報告あり
（濃度一定、水基剤からの透過予測式）

- $K_{o/w}$：水／オクタノール分配係数
- MW：分子量
- R_2, π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$, V_x：
  Abraham Solvation Parameter

定常状態の皮膚透過速度 J_{ss}



$$J_{ss} = \frac{dQ}{dt} = \frac{KC_vD_s}{L_s} = PC_V$$

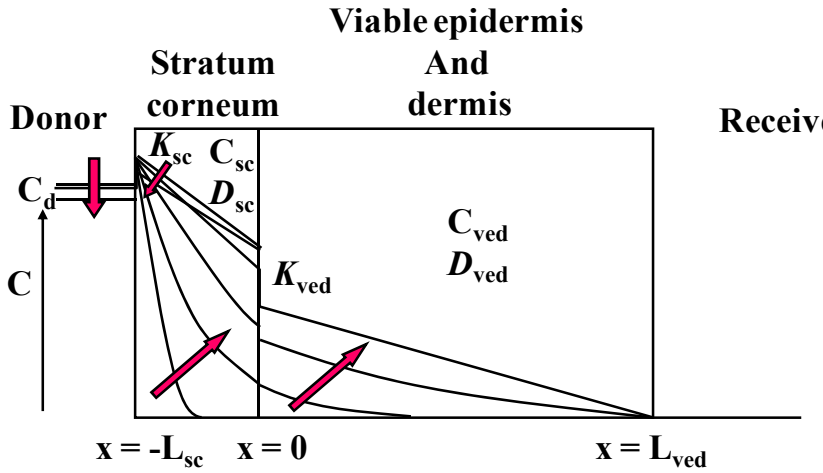
C_v :適用物質濃度

透過係数*P*よりレセプター移行量
（全身循環系移行量の一部）の推定可能

しかし

- 角層下の組織への移行量
  （吸収量＝レセプター移行量＋角層下組織中量）
- 皮膚透過量および皮膚中濃度の経時変化
- TG428条件で適用したとき（ex. <10 μl/cm² :時間の経過に伴い濃度変化あり)の予測は困難

２層膜モデルを用いた皮膚中濃度解析



Csc：sc中濃度
Cved：ved中濃度
Dsc：sc中拡散係数
Dved：ved中拡散係数
Lsc：scの厚み
Lved：vedの厚み
Ksc：sc/donor分配係数
Kved：ved/sc分配係数

sc における位置 x、時間 t の薬物濃度 C_{sc} は Fick の第 2 法則から、

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

ved についても同様に、

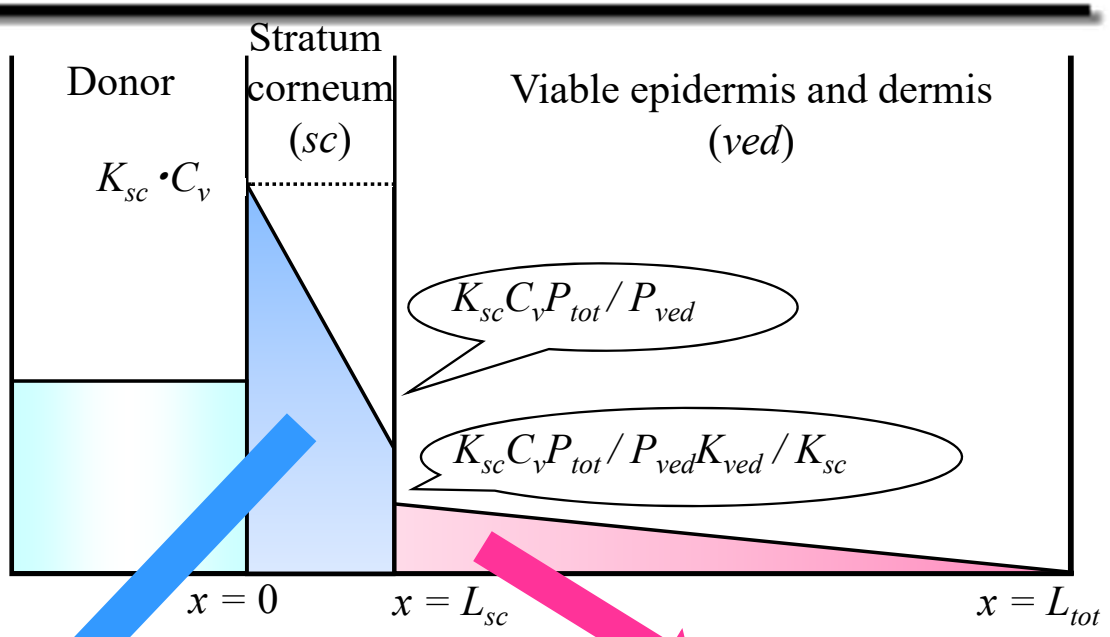
$$\frac{\partial C_{ved}}{\partial t} = D_{ved}\frac{\partial^2 C_{ved}}{\partial x^2}$$

初期条件と境界条件

$t = 0$	$-L_{sc} < x < 0$	$C_{sc} = 0$
	$0 < x < L_{ved}$	$C_{ved} = 0$
$t > 0$	$x = -L_{sc}$	$C_{sc} = K_{sc} \cdot C_d$
	$x = 0$	$C_{ved} = K_{ved} \cdot C_{sc}$
		$D_{sc}\frac{dC_{sc}}{dx} = D_{ved}\frac{dC_{ved}}{dx}$
	$x = L_{ved}$	$C_{ved} = 0$

2層膜の皮膚中平均濃度予測式

K : Partition coefficient
C_v : Donor concentration
L_s : Thickness of membrane
$\overline{C}_{ss}$: Average membrane concentration
P : Permeability coefficient



Conc. in *sc*

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

Conc. in *ved*

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

Conc. in full-thickness skin

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

Sugibayashi K., *et al., Pharm. Res.*, **27**, 134-142 (2010).

Physicochemical properties of model chemical compounds

Drug	Epinepherine (Epi)	Dopamine (Dopa)	Antipyrine (ANP)	Isosorbide mononitrate (ISMN)	Caffeine (CAF)	Aminopyrine (AMP)
M. W.	219.67	189.64	188.22	191.10	194.19	231.29
Clog*P**	-0.684	0.169	0.204	-4.586	-0.04	0.572
p*K*a	8.70, 9.90	2.31, 9.74, 13.40	1.50	—	1.40	5.00

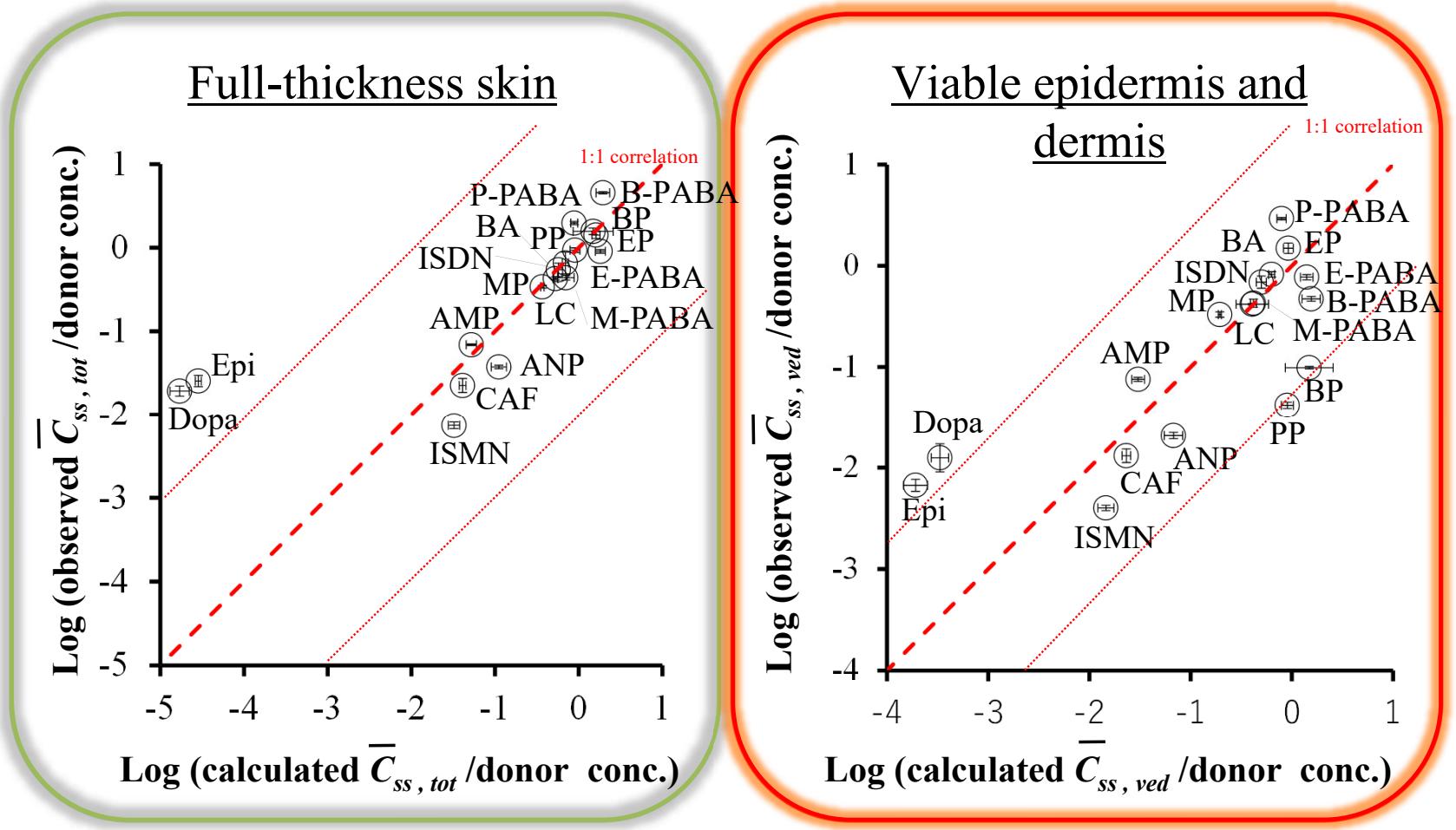
Drug	Isosorbide dinitrate (ISDN)	Methyl PABA (M-PABA)	Lidocaine hydrochloride (LC)	Benzoic acid (BA)	Ethyl PABA (E-PABA)	Methyl paraben (MP)
M. W.	236.10	151.17	234.30	122.12	165.19	152.15
Clog*P**	-5.540	1.394	1.950	1.885	1.932	1.557
p*K*a	—	2.36	7.86	4.20	2.36	8.40

Drug	Ethyl paraben (EP)	Propyl PABA (P-PABA)	Propyl paraben (PP)	Buthyl PABA (B-PABA)	Buthyl paraben (BP)
M. W.	166.18	179.22	180.20	193.24	194.23
Clog*P**	2.513	2.452	3.042	2.981	3.571
p*K*a	8.40	2.37	8.40	2.37	8.40

**Calculation by Chem Draw Ultra 12.2® (PerkinElmer informatics, Cambridge, U.S.A.)*

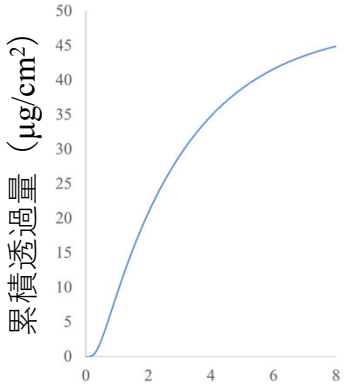
Hydrophilic compounds : Clog*P* < 1 Lipophilic compounds : Clog*P* ≥ 1

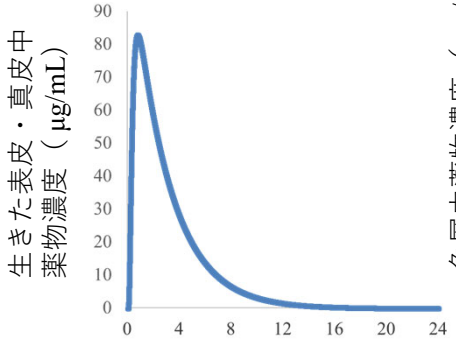
Relationship between calculated skin conc. and observed skin conc.

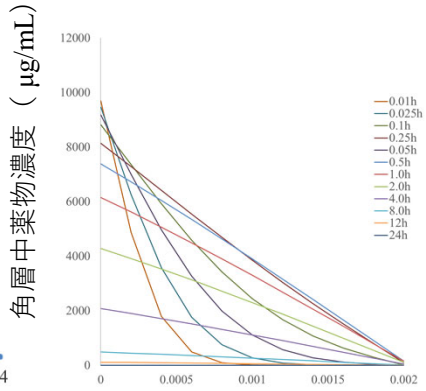


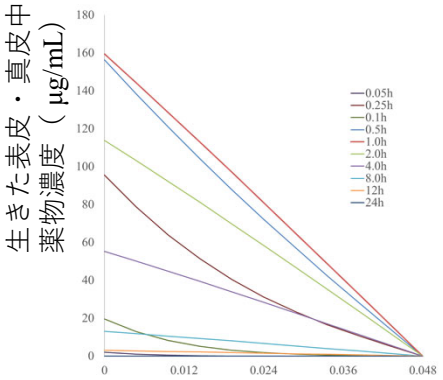
Data range: 122.12<*M.W.*<234.30, -5.54<Clog*P*<3.57 Mean ± S.E. (n = 4)

1.0%, 10 μL/cm^2 P_{sc}: 5×10^{-7} cm/s K_{sc}:1.0 24 h塗布
P_{ved}: 2×10^{-5} cm/s K_{ved}:1.0

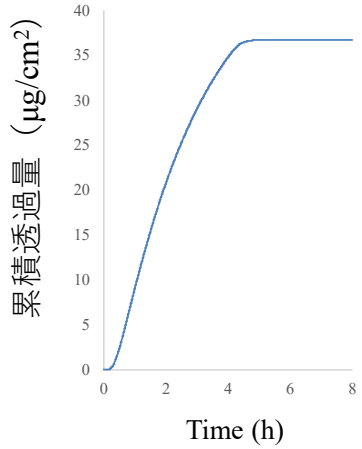


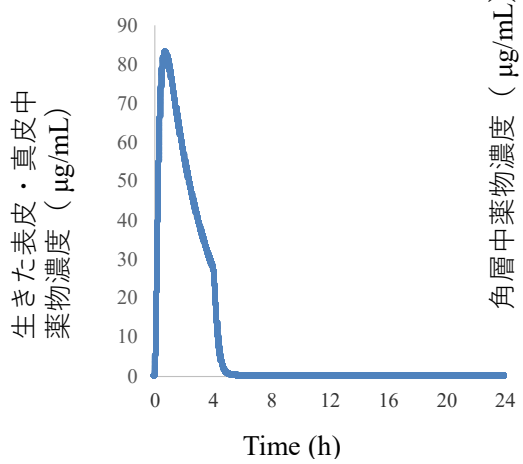


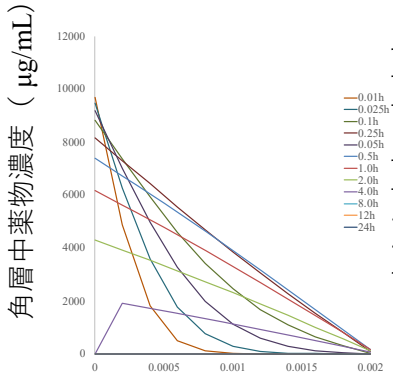


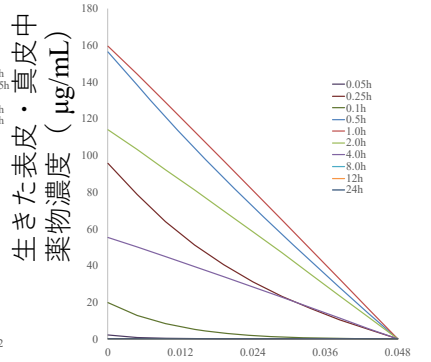


1.0%, 10 μL/cm^2 P_{sc}: 5×10^{-7} cm/s K_{sc}:1.0 4 h塗布、製剤を丁寧に取り除いた場合
P_{ved}: 2×10^{-5} cm/s K_{ved}:1.0









Method

Toxicology in Vitro 69 (2020) 104990

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: 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[a,*], Kevin O. Tankersley[a], Cindy M. Obringer[a], Greg J. Carr[a], John Manwaring[a,1], Helga Rothe[b,2], Hélène Duplan[c], Camille Géniès[c], Sébastien Grégoire[d], Nicola J. Hewitt[e], Carine Jacques Jamin[c], Martina Klaric[e,3], Daniela Lange[f], Alexandra Rolaki[e], Andreas Schepky[f]

[a] The Procter and Gamble Company, Cincinnati, OH, United States of America
[b] Procter and Gamble, Darmstadt, Germany
[c] Pierre Fabre Dermo-Cosmétique, Toulouse, France
[d] L'Oreal Research and Innovation, Aulnay-Sous-Bois, France
[e] ADME Task Force, Cosmetics Europe, Brussels, Belgium
[f] 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.

Cosmetics EuropeのADME タスクフォースから報告されている論文データを引用

➢ 化学物質の物理化学的パラメーターの算出

SCIGRESS

- 分子量（*M.W.*）
- Clog*P*
- HOMO
- LUMO
- HOMO-LUMO Gap
- 融点
- *pKa*
- 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
- 化学ポテンシャル

JMP proにて解析を実施した。

Material

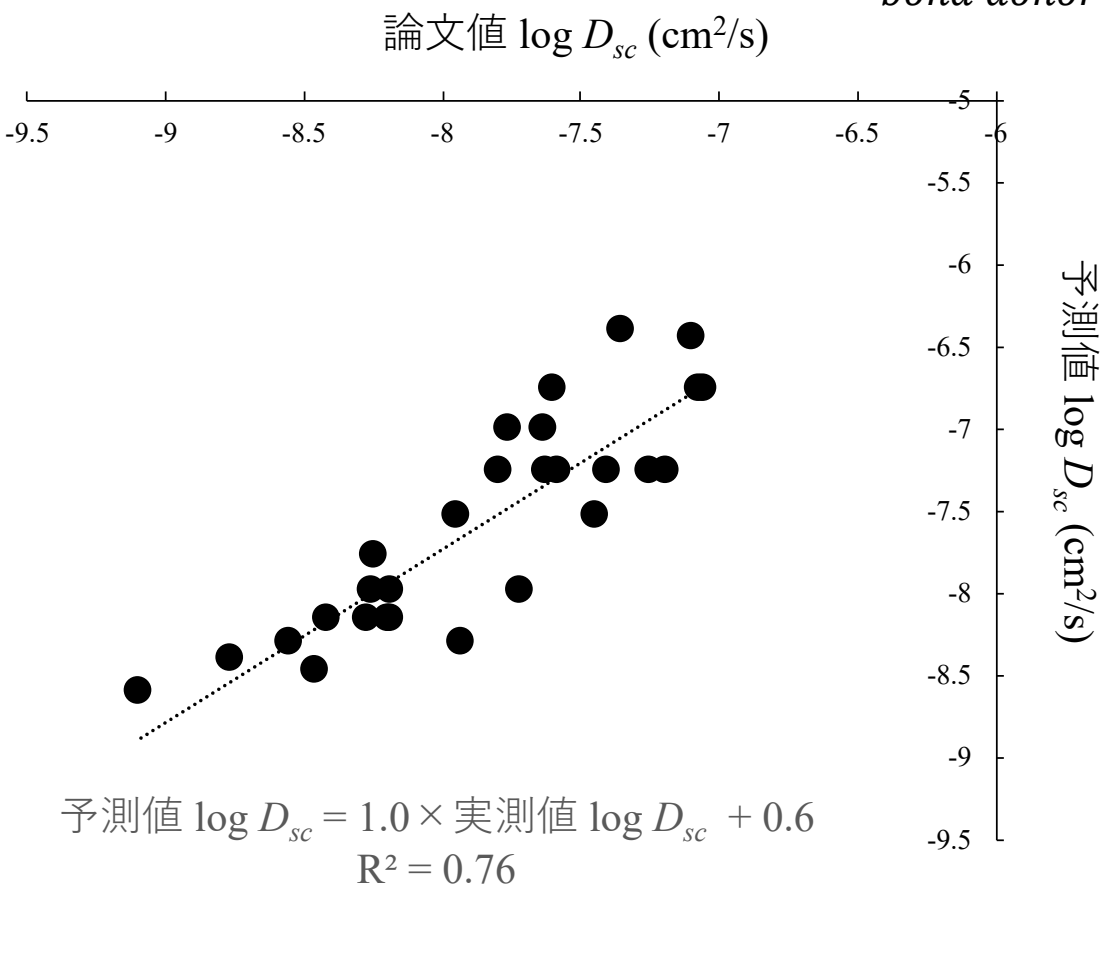
Compound	*M.W.*	ClogP
2,4'-Dichloroacetophenone	189.04	2.7
2,4-Dinitrochlorobenzene	202.55	2.3
2,5-Diaminotoluene	122.17	0.6
2-Acetylaminofluorene	223.27	3.3
2-Ethylhexyl acrylate	184.27	3.8
2-Nitro-P-phenylenediamine	153.14	0.5
3-Methyl-3H-imidazo[4,5-f]quinolin-2-amine	198.22	1.5
4-Amino-3-nitrophenol	154.12	0.9
4-Aminophenol	109.13	0
4-Bromophenyl Isocyanate	198.02	3.4
4-Chloroaniline	127.57	1.9
4-Chlorobutyric acid	122.55	0.6
4-Methylpentanoic acid	116.16	1.4
4-Nitro-o-phenylenediamine	153.14	0.9
6-Methylcoumarin	160.17	1.8
Acetophenone	120.15	1.6
AMP(Aminopyrine)	231.29	1
ANP(Antipyrine)	188.23	0.4
B-PABA(Butyl 4-aminobenzoate)	193.24	2.9
BA(Benzoic acid)	122.12	1.9
Basic Red 76	336.4	4.5
Benzophenone	182.22	3.4
Benzyl bromide	171.03	2.9
Benzylideneacetone	146.19	2.1
BP(Butylparaben)	194.23	3.6

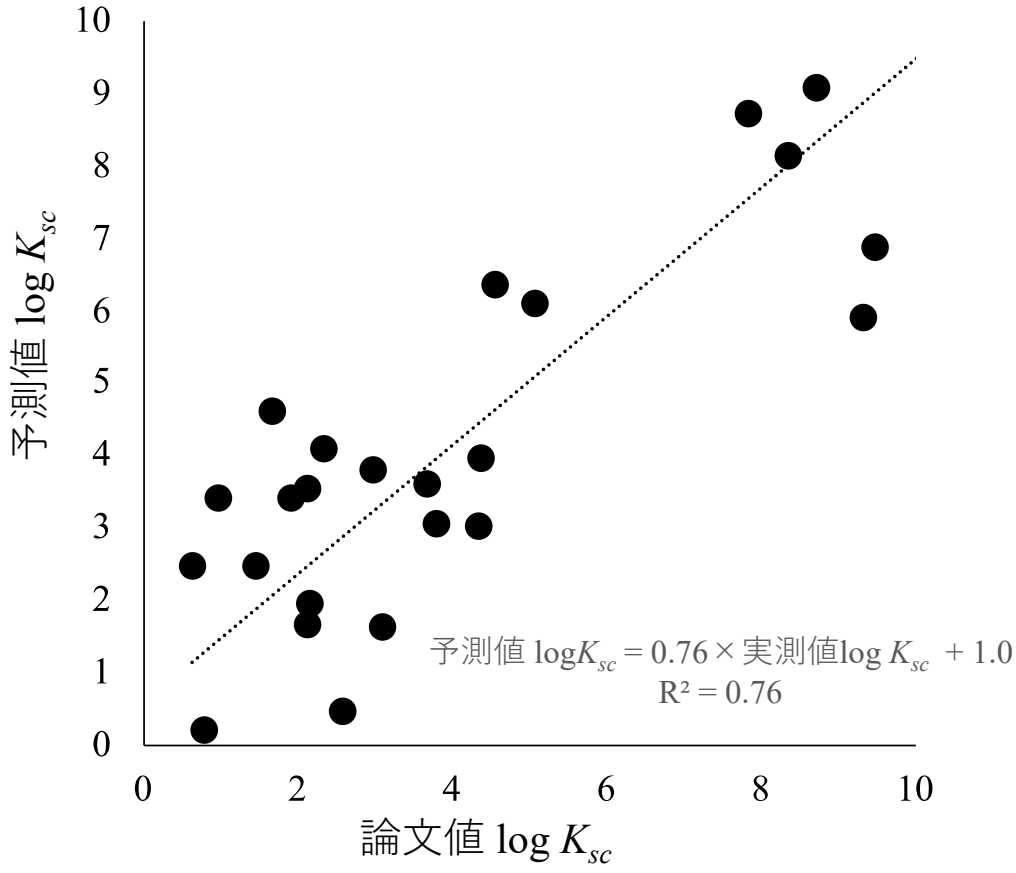
Compound	*M.W.*	ClogP
Butyldiglycol	162.23	0.6
CAF(Caffeine)	194.19	-0.1
Cinnamaldehyde	132.16	1.9
Cinnamic acid	148.16	2.1
Cinnamyl alcohol	134.17	1.9
Cyclophosphamide monohydrate	261.08	0.6
Diethyl maleate	172.18	0.9
Dimethyl phthalate	194.18	1.6
DOPA(Dopamine hydrochloride)	153.18	-1
E-PABA(Ethyl 4-aminobenzoate)	165.19	1.9
EP(Ethylparaben)	166.17	2.5
Epi(Epinephrine)	183.2	-1.4
Ethylumbelliferone	190.19	2.3
Eugenol	164.2	2
Geraniol	154.25	2.9
HC Red No.3	197.19	0.5
Hydrocortisone	362.5	1.6
hydroquinone	110.11	0.6
Ibuprofen	206.28	3.5
ISDN(Isosorbide dinitrate)	236.14	1.3
ISMN(Isosorbide mononitrate)	191.14	-0.4
Isoeugenol	164.2	2.6
Ketoprofen	254.28	3.1

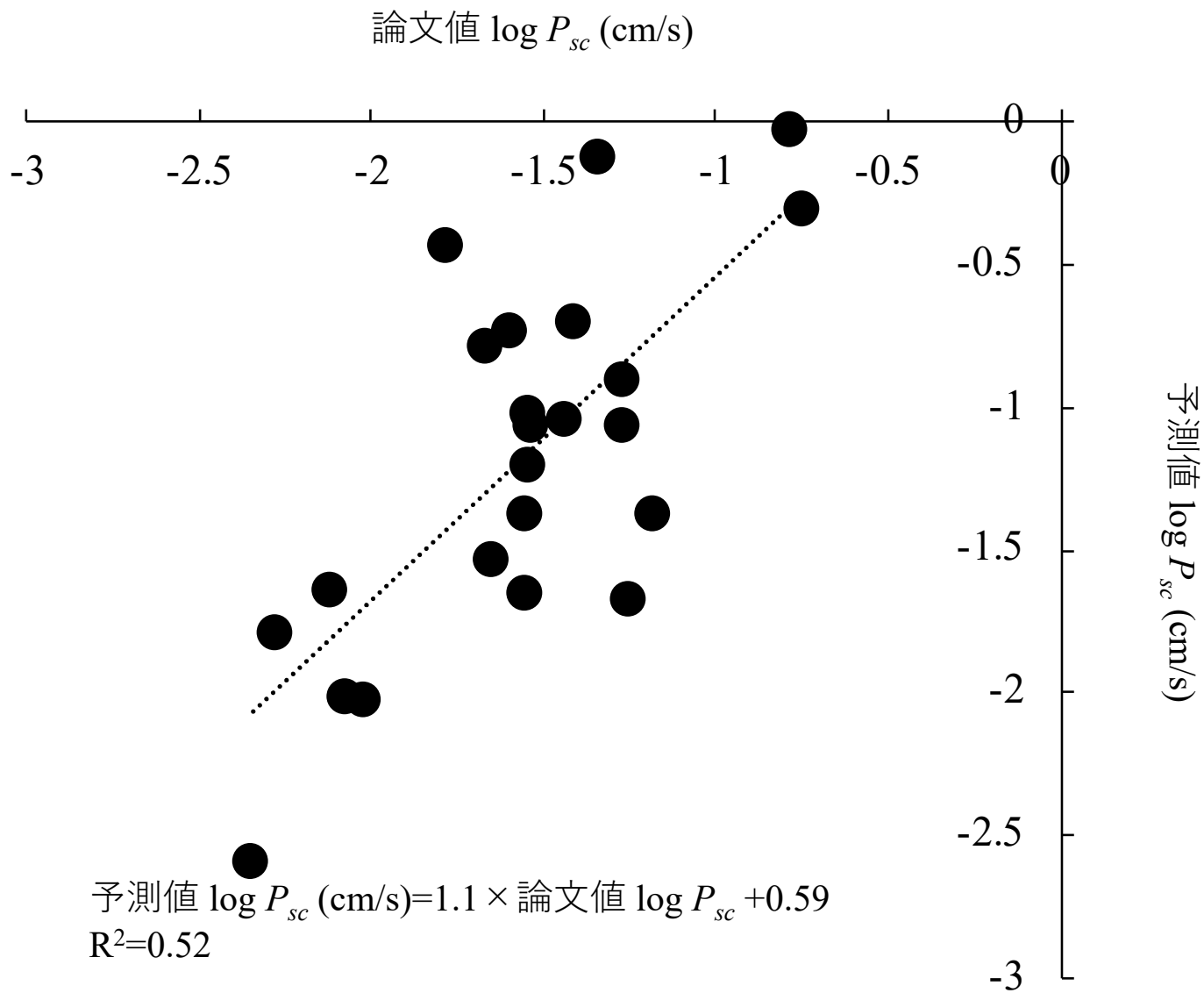
Compound	M.W.	ClogP
lidocaine	234.34	2.3
M-PABA(Methyl 4-aminobenzoate)	151.16	1.4
Methyl methanesulfonate	110.13	-0.4
MP(Methylparaben)	152.15	2
Naphthalene	128.17	3.3
Nitrobenzene	123.11	1.9
Norepinephrine	169.18	-1.2
P-PABA(propyl 4-aminobenzoate)	179.22	2.4
p-Phenylenediamine	108.14	-0.3
p-Tolunitrile	117.15	2.4
PP(propylparaben)	180.2	3
Resorcinol	110.11	0.8
Salicylic acid	138.12	2.3
Testosterone	288.4	3.3
Thioglycolic acid	92.12	0.1
Tetramethyl thiuram disulfide	240.4	1.7
Triclosan	289.5	5
Vanillin	152.15	1.2

予測値$D_{sc} = 2.2 \times \exp\left(-\frac{(ClogP - 2.4)^2}{0.5}\right) - 8.6$

予測値$logK_{sc}$
$= 5.1\ ClogP - 1.3LUMO - HOMOgap - 2.5 \times 10^{-3} melting\ point$
$+ 0.51 dipole\ moment + 2.0 chemical\ potential + 2.3(LUMO - HOMOgap$
$\times (chemical\ potential - 5.0) - 1.8 \times 10^{-3}(melting\ point - 67) \times (H$
$- bond\ donor - 0.63)$



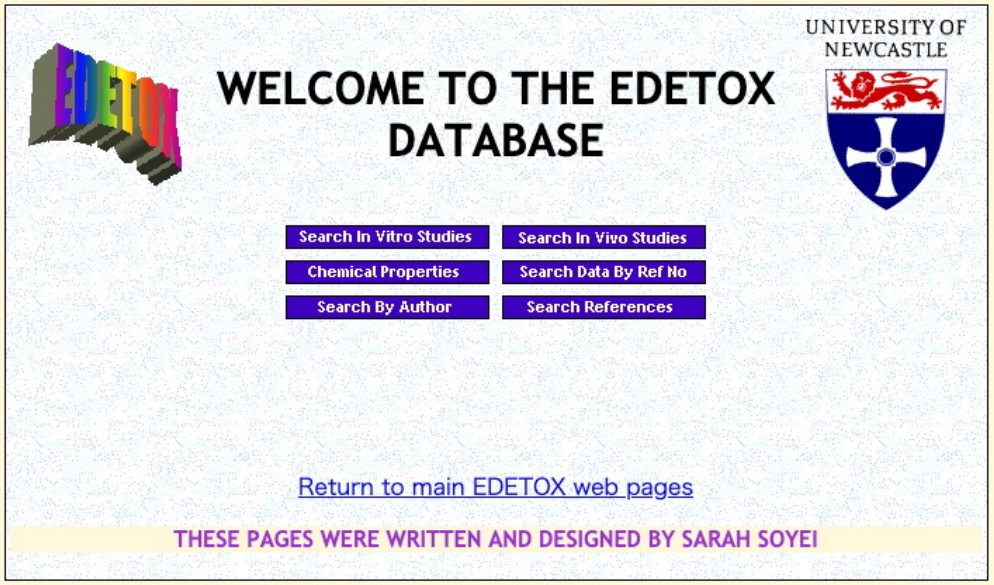



論文値 log P_{sc} (cm/s)
-3
-2.5
-2
-1.5
-1
-0.5
0
0
-0.5
-1
-1.5
-2
-2.5
-3
予測値 log P_{sc} (cm/s)
予測値 log P_{sc} (cm/s)=1.1 × 論文値 log P_{sc} +0.59
R^2=0.52

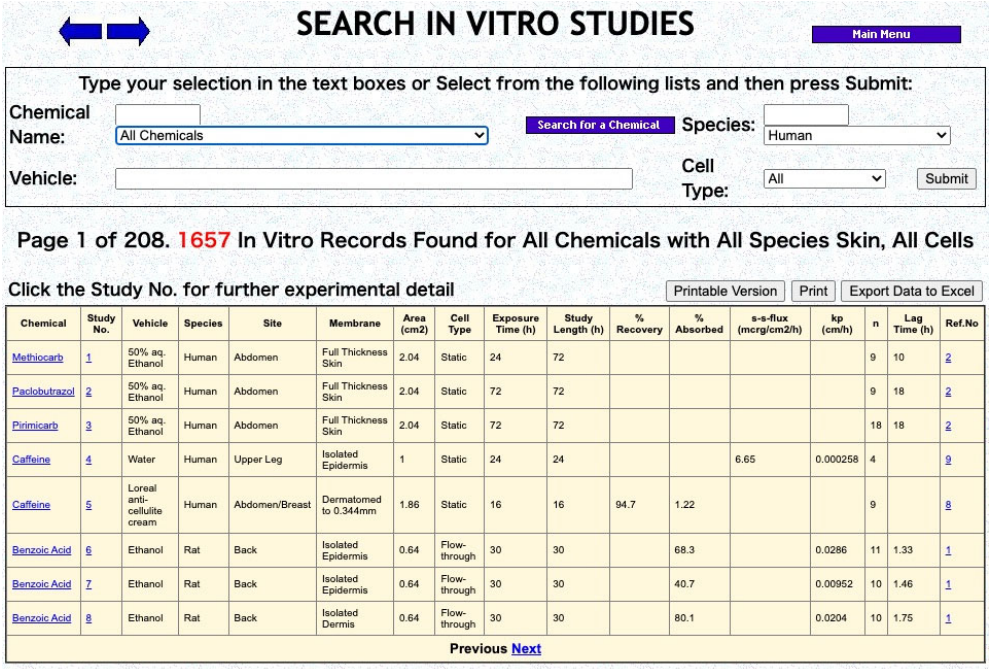
Future plan

各パラメータの予測モデルの構築後
　水基材からの化学物質の皮膚透過性および吸収性に関して、予測モデルの妥当性を検証する

予測モデルの妥当性に関しては、OECD皮膚吸収性試験ガイドライン及びガイダンス作成にするにあたり、
実施された試験を収集したデータベースEDETOX database (https://apps.ncl.ac.uk/edetox/)を用いる。



EDETOX database



Chemical	Study No.	Vehicle	Species	Site	Membrane	Area (cm2)	Cell Type	Exposure Time (h)	Study Length (h)	% Recovery	% Absorbed	s-s-flux (mcrg/cm2/h)	kp (cm/h)	n	Lag Time (h)	Ref.No
Methiocarb	1	50% aq. Ethanol	Human	Abdomen	Full Thickness Skin	2.04	Static	24	72					9	10	2
Paclobutrazol	2	50% aq. Ethanol	Human	Abdomen	Full Thickness Skin	2.04	Static	72	72					9	18	2
Pirimicarb	3	50% aq. Ethanol	Human	Abdomen	Full Thickness Skin	2.04	Static	72	72					18	18	2
Caffeine	4	Water	Human	Upper Leg	Isolated Epidermis	1	Static	24	24			6.65	0.000258	4		9
Caffeine	5	Loreal anti-cellulite cream	Human	Abdomen/Breast	Dermatomed to 0.344mm	1.86	Static	16	16	94.7	1.22			9		8
Benzoic Acid	6	Ethanol	Rat	Back	Isolated Epidermis	0.64	Flow-through	30	30		68.3		0.0286	11	1.33	1
Benzoic Acid	7	Ethanol	Rat	Back	Isolated Epidermis	0.64	Flow-through	30	30		40.7		0.00952	10	1.46	1
Benzoic Acid	8	Ethanol	Rat	Back	Isolated Dermis	0.64	Flow-through	30	30		80.1		0.0204	10	1.75	1

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