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Original Article

Artificial neural network analysis for predicting human percutaneous absorption taking account of vehicle properties

Tomomi Atobe[1], Masaaki Mori[1], Fumiyoshi Yamashita[2], Mitsuru Hashida[2] and Hirokazu Kouzuki[1]

[1]Shiseido Research Center, Shiseido Co., Ltd., 2-2-1 Hayabuchi, Tsuzuki-ku, Yokohama 224-8558, Japan
[2]Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University, 46-29 Yoshidashimoadachi-cho, Sakyo-ku, Kyoto 606-8501, Japan

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ABSTRACT — An *in silico* method for predicting percutaneous absorption of cosmetic ingredients was developed by using artificial neural network (ANN) analysis to predict the human skin permeability coefficient (log K_p), taking account of the physicochemical properties of the vehicle, and the apparent diffusion coefficient (log D). Molecular weight and octanol-water partition coefficient (log P) of chemicals, and log P of the vehicles, were used as molecular descriptors for predicting log K_p and log D of 359 samples, for which literature values of either or both of log K_p and log D were available. Adaptivity of the ANN model was evaluated in comparison with a multiple linear regression model (MLR) by calculating the root-mean-square (RMS) errors. Accuracy and robustness were confirmed by 10-fold cross-validation. The predictive RMS errors of the ANN model were smaller than those of the MLR model (log K_p; 0.675 vs 0.887, log D; 0.553 vs 0.658), indicating superior performance. The predictive RMS errors for log K_p and log D with the ANN model after 10-fold cross-validation analysis were 0.723 and 0.606, respectively. Moreover, we estimated the cumulative amounts of chemicals permeated into the skin during 24 hr (Q24hr) from the values of log K_p and log D by applying Fick's law of diffusion. Our results suggest that this newly established ANN analysis method, taking account of the property of the vehicle, could contribute to non-animal risk assessment of cosmetic ingredients by providing a tool for calculating Q24hr, which is required for evaluating the margin of safety.

Key words: Percutaneous absorption, Risk assessment, *In silico*, Artificial neural network, Vehicle

INTRODUCTION

Evaluation of percutaneous absorption, which can be defined as the transfer of a compound from the surface of the stratum corneum to the systemic circulation through the skin, is important for risk assessment of cosmetic products and medicines for external use, not only for systemic toxicities such as acute toxicity, genotoxicity, reproductive toxicity, developmental toxicity and carcinogenicity, but also for local toxicities such as skin irritation, skin sensitization and eye irritation. The risk assessment of chemicals is often based on the margin of safety (MoS) approach (Scientific Committee on Consumer Safety (SCCS), 2012). Calculation of the MoS requires knowledge of the values of the no observable adverse effect level (NOAEL), which is the highest dose not resulting in observable adverse effects, and the systemic exposure dosage (SED), which is the amount of the chemical that is expected to enter the bloodstream. The MoS is expressed as the ratio of the NOAEL to the SED. If the MoS exceeds 100 (safety threshold), the compound is generally regarded as safe for human use. In the risk assessment of cosmetic ingredients, NOAEL used to be obtained by means of repeated-dose oral toxicity study, while the SED was obtained from percutaneous absorption studies in animals.

However, in the European Union (EU), a ban on marketing of cosmetics tested in animals was enforced by the 7th amendment of the EU cosmetics directive on March 11, 2013 (The EU, 2013). Consequently, a range of *in*

Correspondence: Hirokazu Kouzuki (E-mail: hirokazu.kouzuki@to.shiseido.co.jp)

vitro methods has had to be developed, including methods for prediction of *in vivo* skin permeability, under the aegis of the European Centre for the Validation of Alternative Methods (ECVAM) in the EU, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in the United States and the Japanese Centre for the Validation of Alternative Methods (JaCVAM) in Japan. An *in vitro* percutaneous absorption test (OECD, 2004b) and various other *in vitro* test methods have been included in the OECD test guidelines as alternatives to animal tests (OECD, 1997, 2004a, 2013a, 2013b, 2013c, 2014a, 2014b). However, there are concerns about studies using *in vitro* methods, including cost, time and the need for the validation of analysis.

Thus, there is increasing interest in *in silico* prediction methods. Already, *in silico* methods have been developed for the prediction of toxicological responses such as skin sensitization (Teubner *et al.*, 2013) and repeated-dose toxicity (Venkatapathy *et al.*, 2004). As for percutaneous absorption, Potts and Guy (1992) have predicted skin permeability coefficient (log K_p) from the molecular weight and octanol-water partition coefficient (log *P*) of chemicals. Barratt (1995) developed a quantitative structure-activity relationship (QSAR) methodology for prediction of skin permeability by inclusion of melting point as an independent variable, together with log *P* and molecular volume. Saini *et al.* (2010) developed a method for predicting the skin permeability of chemicals by artificial neural network (ANN) analysis of log K_p and Abraham descriptors. Lim *et al.* (2002) predicted the skin permeability of chemicals from their three-dimensional molecular structure using a combination of molecular orbital calculation and ANN analysis. Chen *et al.* (2007) also developed a method for predicting skin permeability of chemicals by using a combination of Abraham descriptors and ANN analysis. Ghafourian *et al.* (2010) predicted skin permeation using parameters that included physicochemical properties of the vehicle. However, there is still no comprehensive algorithm that can predict human percutaneous permeation, taking account of the physicochemical properties of the vehicle, using simple and intuitive descriptors of both the diffusion and partitioning aspects of permeation.

In this context, we focused on the use of simple molecular descriptors of chemicals and vehicles, and we selected molecular weight (*MW*) and log *P*, which are known to be relevant to skin permeation (Potts and Guy, 1992). We then collected a large dataset of values referring to human skin from the literature to create a model with high generality. We used this dataset to develop an ANN model for predicting log K_p, which is influenced by the physicochemical properties of vehicles, and apparent diffusion coefficient (log *D*), because these parameters can be used to calculate the cumulative amounts of chemicals permeated into the skin during 24 hr (*Q*24hr) according to Fick's law of diffusion.

MATERIALS AND METHODS

Dataset

Human skin percutaneous absorption data were collected from the literature (Table 1). The dataset covers structurally diverse penetrants, including hydrocarbons, alcohols, aldehydes, ketones, ethers, esters, carboxylic acids, amines and amides, which were dissolved in various pure and mixed solvents. The log K_p and log *D* values were taken from the literature or obtained by calculation from parameters or descriptors in the literature. This dataset included 359 samples with data for log K_p and 107 samples with data for log *D*.

Calculation of physicochemical properties

The molecular weight (*MW*) of chemicals (MW_c), log *P* of chemicals (log P_c) and log *P* of vehicles (log P_v) were calculated using Pallas Ver. 3.1 (CompuDrug International Inc., South San Francisco, CA, USA). Some vehicles were mixtures of two or three components. The MW_c, log P_c and log P_v of such blended vehicles were calculated as volume-weighted averages, according to Ghafourian *et al.* (2010).

Multiple linear regression analysis

Multiple linear regression was used for log K_p and log *D* as the dependent variables with molecular descriptors *MW*, log P_c and log P_v. The predictivity was evaluated by a 10-fold cross-validation procedure. The samples were divided into ten groups at random. Regression analysis was performed 10 times, each time leaving one group out. The values of the test sets of log K_p or log *D* were estimated using the equations obtained from the training sets in the analysis. The difference between the observed and the predicted log K_p or log *D* values was evaluated by the goodness-of-fit of the root-mean-square (RMS) error. The RMS error was defined as follows:

$$\text{RMS error} = \sqrt{\sum((\text{measured value} - \text{predicted value})^2)/\text{number of data}}$$

ANN analysis

A feed-forward 3-layered neural network (Hirota *et al.*, 2013) was used in this analysis as reported previously. This network consists of an input layer, a hidden layer, and an output layer. All the calculations were performed

Table 1. Chemical name, MW_c, log P_c, log P_v, log K_p and log D of compounds used in the study.

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Water	18.02	-1.31	-1.31	Water	-3.70	-6.05	1
Water	18.02	-1.31	-1.31	Water	-3.30	-5.69	1
Methanol	32.05	-0.49	-0.49	Undiluted solution	-1.98	-4.21	1
Methanol	32.05	-0.49	-1.31	Water	-3.30	-5.65	1
Ethanol	46.08	-0.02	-0.02	Undiluted solution	-3.14	-5.19	1
Ethanol	46.08	-0.02	-1.31	Water	-3.10	-5.62	1
Propanol	60.11	0.36	0.36	Undiluted solution	-3.80	-5.54	1
Propanol	60.11	0.36	-1.31	Water	-2.92	-5.54	1
Butanol	74.14	0.84	0.84	Undiluted solution	-4.22	-6.27	1
Butanol	74.14	0.84	-1.31	Water	-2.60	-5.57	1
Pentanol	88.17	1.38	1.38	Undiluted solution	-4.29	-6.08	1
Pentanol	88.17	1.38	-1.31	Water	-2.22	-5.50	1
Hexanol	102.20	1.94	1.94	Undiluted solution	-4.28	-5.86	1
Hexanol	102.20	1.94	-1.31	Water	-1.89	-5.46	1
Heptanol	116.23	2.49	2.49	Undiluted solution	-4.60	-6.14	1
Heptanol	116.23	2.49	-1.31	Water	-1.49	-5.55	1
Octanol	130.26	3.02	3.02	Undiluted solution	-5.00	-6.21	1
Octanol	130.26	3.02	-1.31	Water	-1.28	-5.56	1
Nonanol	144.29	3.55	3.55	Undiluted solution	-5.52	N.D.	1
Nonanol	144.29	3.55	-1.31	Water	-1.22	N.D.	1
Decanol	158.32	4.10	4.10	Undiluted solution	-6.10	N.D.	1
Decanol	158.32	4.10	-1.31	Water	-1.10	N.D.	1
Phenol	94.12	1.59	-1.31	Water	-2.09	-4.83	2
o-Cresol	108.15	2.11	-1.31	Water	-1.80	-4.83	2
m-Cresol	108.15	2.09	-1.31	Water	-1.82	-4.83	2
p-Cresol	108.15	1.95	-1.31	Water	-1.76	-4.86	2
Resorcinol	110.12	0.70	-1.31	Water	-3.62	-5.56	2
3,4-Xylenol	122.18	2.49	-1.31	Water	-1.44	-4.86	2
m-Nitrophenol	139.12	1.67	-1.31	Water	-2.25	-5.36	2
Chlorocresol	142.59	3.06	-1.31	Water	-1.26	-4.89	2
β-Naphthol	144.18	2.83	-1.31	Water	-1.55	-5.13	2
Thymol	150.24	3.30	-1.31	Water	-1.28	-4.91	2
Chloroxylenol	156.62	3.55	-1.31	Water	-1.23	-4.91	2
p-Bromophenol	173.01	2.67	-1.31	Water	-1.44	-4.83	2
p-Ethylphenol	122.18	2.40	-1.31	Water	-1.46	N.D.	2
o-Chlorophenol	128.56	2.32	-1.31	Water	-1.48	N.D.	2
p-Chlorophenol	128.56	2.42	-1.31	Water	-1.44	N.D.	2
p-Nitrophenol	139.12	1.86	-1.31	Water	-2.25	N.D.	2
Methylhydroxybenzoate	152.16	2.39	-1.31	Water	-2.04	N.D.	2
2,4-Dichlorophenol	163.00	3.16	-1.31	Water	-1.22	N.D.	2
2,4,6-Trichlorophenol	197.44	3.71	-1.31	Water	-1.23	N.D.	2
Phenylethylamine	121.20	0.60	-1.31	Water	-3.77	-6.75	3
Salicylic acid	138.13	1.57	-1.31	Water	-4.22	-6.29	3
Mannitol	182.20	-2.89	-1.31	Water	-4.30	-6.36	3

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Estrone	270.40	4.07	-1.31	Water	-2.44	-6.50	4
Estradiol	272.42	3.83	-1.31	Water	-3.52	-7.58	4
Estriol	288.42	2.58	-1.31	Water	-4.40	-8.16	4
Testosterone	288.47	3.43	-1.31	Water	-3.40	-7.15	4
Progesterone	314.51	3.29	-1.31	Water	-2.82	-7.24	4
Pregnenolone	316.53	3.61	-1.31	Water	-2.82	-7.10	4
Cortexone	330.51	3.15	-1.31	Water	-3.35	-7.31	4
Hydroxyprogesterone	330.51	2.74	-1.31	Water	-3.22	-7.22	4
Hydroxypregnenolone	332.53	2.36	-1.31	Water	-3.22	-7.25	4
Cortexolone	346.51	2.73	-1.31	Water	-4.12	-7.89	4
Corticosterone	346.51	2.45	-1.31	Water	-4.22	-7.85	4
Aldosterone	360.49	1.29	-1.31	Water	-5.52	-8.75	4
Cortisone	360.49	2.08	-1.31	Water	-5.00	-8.33	4
Hydrocortisone	362.51	1.73	-1.31	Water	-5.52	-8.76	4
2-Butanone	72.12	0.68	-1.31	Water	-2.35	-5.44	5, 6
1-Butanol	74.14	0.84	-1.31	Water	-2.52	-5.44	5, 6
Ethylether	74.14	1.26	-1.31	Water	-1.80	-5.44	5, 6
2,3-Butanediol	90.14	-0.03	-1.31	Water	-4.30	-6.44	5, 6
2-Ethoxyethanol	90.14	-0.18	-1.31	Water	-3.60	-6.44	5, 6
Propanol	60.11	0.36	-1.31	Water	-2.77	N.D.	5
Heptanol	116.23	2.49	-1.31	Water	-1.42	N.D.	5
Haloperidol	375.9	4.12	-1.31	Water	-3.47	-6.50	7
Nicotine	162.26	1.34	-1.31	Water	-3.23	-5.76	8
Meperidine	247.37	2.60	-1.31	pH 7.4 Buffer	-2.43	-6.85	9
Hydromorphine	285.37	1.26	-1.31	pH 7.4 Buffer	-4.82	-7.77	9
Morphine	285.37	0.70	-1.31	pH 7.4 Buffer	-5.03	-7.49	9
Codeine	299.40	0.79	-1.31	pH 7.4 Buffer	-4.31	-7.66	9
Fentanyl	336.52	4.07	-1.31	pH 7.4 Buffer	-2.25	-7.06	9
Sufentanil	386.60	3.63	-1.31	pH 7.4 Buffer	-1.92	-7.08	9
Sufentanil	386.60	3.63	-1.31	pH 7.4 Buffer	-2.26	-5.61	10
Fentanyl	336.52	4.07	-1.31	pH 7.4 Buffer	-2.52	-4.82	10
Etorphine	411.59	2.10	-1.31	pH 7.4 Buffer	-2.44	-5.98	11
Water	18.02	-1.31	-0.52	Glycerol triacetate	-1.66	-5.10	12
Water	18.02	-1.31	0.00	Propylene carbonate : Glycerol triacetate = 70 : 30	-1.73	-5.16	12
Water	18.02	-1.31	0.22	Propylene carbonate	-2.20	-4.85	12
Water	18.02	-1.31	0.35	*n*-Butyl acetate : Propylene carbonate = 10 : 90	-1.76	-5.12	12
Water	18.02	-1.31	0.62	*n*-Butyl acetate : Propylene carbonate = 30 : 70	-1.61	-5.21	12
Water	18.02	-1.31	0.76	Isobutanol	-1.64	-4.32	12
Water	18.02	-1.31	0.88	2-Butanol	-1.76	-4.34	12
Water	18.02	-1.31	1.15	Cyclohexanone	-1.39	-4.36	12
Water	18.02	-1.31	1.27	*n*-Butyl lactate	-1.92	-4.59	12
Water	18.02	-1.31	1.27	Cyclohexanol	-1.89	-4.81	12
Water	18.02	-1.31	1.50	Methyl isobutyl ketone	-0.99	-4.89	12
Water	18.02	-1.31	1.52	Methyl *n*-butyl ketone	-1.03	-4.94	12

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Water	18.02	-1.31	1.56	*n*-Butyl acetate	-0.80	-4.81	12
Water	18.02	-1.31	1.73	Methyl isobutyl carbinol	-1.17	-4.24	12
Water	18.02	-1.31	2.10	Amyl acetate	-0.82	-4.93	12
Water	18.02	-1.31	2.19	Isophorone	-1.40	-4.69	12
Water	18.02	-1.31	4.10	*n*-Decanol	-1.34	-4.89	12
Benzene	78.12	2.09	-1.31	Water	-0.95	-4.83	13
Benzene	78.12	2.09	3.60	Hexane	-2.62	-4.16	13
Benzene	78.12	2.09	4.46	Isooctane	-2.43	-4.06	13
Benzene	78.12	2.09	8.72	Hexadecane	-3.03	-4.70	13
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.75	Polyethylene glycol 400 : Water : *N,N*-diethyl-*m*-toluamide = 60 : 30 : 10	-3.92	-7.16	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.71	Polyethylene glycol 400 : Water : *N,N*-diethyl-*m*-toluamide = 75 : 15 : 10	-3.98	-7.36	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.64	Propylene glycol : Water : *N,N*-diethyl-*m*-toluamide = 45 : 45 : 10	-3.24	-7.88	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.57	Polyethylene glycol 400 : Propylene glycol : *N,N*-diethyl-*m*-toluamide = 60 : 30 : 10	-4.14	-7.95	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.55	Propylene glycol : Water : *N,N*-diethyl-*m*-toluamide = 60 : 30 : 10	-3.22	-8.00	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.46	Propylene glycol : Water : *N,N*-diethyl-*m*-toluamide = 75 : 15 : 10	-3.84	-7.95	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	-0.37	Propylene glycol : *N,N*-diethyl-*m*-toluamide = 90 : 10	-4.00	-7.90	14
N,N-Diethyl-*m*-toluamide	191.30	2.67	2.67	Undiluted solution	N.D.	-7.76	14
Ketorolac acid	259.33	1.02	-0.71	Propylene glycol	-4.41	-6.44	15
Ketorolac acid	259.33	1.02	-0.49	Propylene glycol : Glycerol monocaprylate = 90 : 10	-3.14	-6.04	15
β-Estradiol	272.42	3.83	-0.34	Ethanol : Water = 75 : 25	-3.00	-4.94	16
β-Estradiol	272.42	3.83	0.08	Ethanol : Water : Oleic acid = 75 : 20 : 5	-2.00	-4.13	16
Physostigmine	275.39	2.27	0.12	Propionic acid	-4.59	-6.17	17
Physostigmine	275.39	2.27	3.23	Propylene glycol : Oleic acid = 50 : 50	-3.98	-6.37	17
Physostigmine	275.39	2.27	3.65	Propionic acid : Oleic acid = 50 : 50	-4.02	-6.21	17
Physostigmine	275.39	2.27	3.87	Propionic acid : Isopropyl myristate = 50 : 50	-4.16	-6.11	17
Physostigmine	275.39	2.27	6.47	Propionic acid : Oleic acid = 10 : 90	-5.08	-6.27	17
Haloperidol	375.9	4.12	-0.71	Propylene glycol	-4.26	-6.38	18
Haloperidol	375.9	4.12	-0.67	Ethanol : Water = 50 : 50	-3.07	-6.42	18
N-Nitrosodiethanolamine	134.16	-1.31	7.61	Isopropyl myristate	-2.39	-6.17	19
N-Nitroso-*N*-methyldodecylamine	228.43	4.86	7.61	Isopropyl myristate	-5.05	-6.09	19
Terbutaline	225.32	0.94	-0.71	Propylene glycol	-3.72	-6.46	20
Diazepam	284.76	2.77	-0.02	Ethanol	-1.97	-5.77	21
Water	18.02	-1.31	-1.31	Undiluted solution	-2.81	N.D.	22
2-Propoxyethanol	104.17	0.23	0.23	Undiluted solution	-3.19	N.D.	22
2-Ethylhexanol	130.26	2.8	2.8	Undiluted solution	-4.34	N.D.	22
2-Ethoxyethyl acetate	132.18	0.62	0.62	Undiluted solution	-2.84	N.D.	22
Ethyl 3-ethoxy-propionate	146.21	1.32	1.32	Undiluted solution	-3.11	N.D.	22
Diethylene glycol monobutyl ether	162.26	0.46	0.46	Undiluted solution	-3.51	N.D.	22
Di(2-ethyl-hexyl)phthalate	390.62	6.81	6.81	Undiluted solution	-6.98	N.D.	22
Urea	60.07	-1.06	-1.31	Water	-3.83	N.D.	22
Ephedrine	165.26	0.91	-1.31	Water	-2.22	N.D.	23
Diethylcarbamazine	199.34	0.56	-1.31	Water	-3.89	N.D.	23
Nitroglycerin	227.11	1.40	-1.31	Water	-1.96	N.D.	23
Estradiol	272.42	3.83	-1.31	Water	-2.28	N.D.	23

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Chloropheniramine	274.82	3.67	-1.31	Water	-2.66	N.D.	23
Atropine	289.41	1.89	-1.31	Water	-5.07	N.D.	23
Scopolamine	303.39	1.02	-1.31	Water	-4.30	N.D.	23
Fentanyl	336.52	4.07	-1.31	Water	-2.00	N.D.	23
Ouabain	584.73	-1.77	-1.31	Water	-6.11	N.D.	23
Digitoxin	765.05	2.62	-1.31	Water	-4.89	N.D.	23
Water	18.02	-1.31	-1.31	Water	-2.85	N.D.	24
Hexanol	102.20	1.94	-1.31	Water	-1.56	N.D.	24
o-Phenylenediamine	108.16	0.02	-1.31	Water	-3.35	N.D.	25
p-Phenylenediamine	108.16	-0.19	-1.31	Water	-3.62	N.D.	25
4-Chloro-*m*-phenylenediamine	142.60	1.00	-1.31	Water	-2.68	N.D.	25
2-Nitro-*p*-phenylenediamine	153.16	0.62	-1.31	Water	-3.30	N.D.	25
4-Amino-2-nitrophenol	154.14	0.94	-1.31	Water	-2.55	N.D.	25
2-Amino-4-nitrophenol	154.14	1.10	-1.31	Water	-3.18	N.D.	25
Water	18.02	-1.31	-1.31	Undiluted solution	-3.02	N.D.	26
Ethanol	46.08	-0.02	-1.31	Water	-2.72	N.D.	27
Butanol	74.14	0.84	-1.31	Water	-2.10	N.D.	27
Hexanol	102.20	1.94	-1.31	Water	-1.49	N.D.	27
Octanol	130.26	3.02	-1.31	Water	-1.03	N.D.	27
Decanol	158.32	4.10	-1.31	Water	-1.15	N.D.	27
8-Methoxypsoralen	216.20	2.19	-1.31	Water	-1.75	N.D.	28
Water	18.02	-1.31	-1.31	Undiluted solution	-3.03	N.D.	29
Paraquat	186.28	-3.70	-1.31	Water	-5.15	N.D.	29
Ketorolac	215.32	2.51	-1.31	Water	-2.72	N.D.	30
Ketoprofen	254.30	2.97	-1.31	Water	-2.57	N.D.	30
Diclofenac	296.16	4.45	-1.31	Water	-2.89	N.D.	30
Piroxicam	331.37	1.48	-1.31	Water	-2.85	N.D.	30
Tenoxicam	337.39	1.86	-1.31	Water	-3.05	N.D.	30
Indomethacin	357.81	3.90	-1.31	Water	-3.15	N.D.	30
Water	18.02	-1.31	-1.31	Undiluted solution	-2.80	N.D.	31
Amphetamine	135.23	1.39	-1.31	Water	-4.85	N.D.	31
Estradiol	272.42	3.83	-1.31	Water	-2.41	N.D.	31
Ouabain	584.73	-1.77	-1.31	Water	-5.40	N.D.	31
Water	18.02	-1.31	-1.31	Water	-3.52	N.D.	32
Butanol	74.14	0.84	-1.31	Water	-2.66	N.D.	32
Salicylic acid	138.13	1.57	-1.31	Water	-4.00	N.D.	32
Estradiol	272.42	3.83	-1.31	Water	-2.52	N.D.	32
Sucrose	342.34	-3.21	-1.31	Water	-5.28	N.D.	32
Corticosterone	346.51	2.45	-1.31	Water	-3.52	N.D.	32
Aldosterone	360.49	1.29	-1.31	Water	-4.30	N.D.	32
2-Phenyl ethanol	122.18	1.55	-1.31	Water	-1.54	N.D.	33
2-Phenyl propanol	136.21	1.89	-1.31	Water	-1.28	N.D.	33
2-Phenyl butanol	150.24	2.25	-1.31	Water	-1.19	N.D.	33
2-Phenyl pentanol	164.27	2.69	-1.31	Water	-0.97	N.D.	33

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
2-Phenyl hexanol	178.30	3.23	-1.31	Water	-1.01	N.D.	33
Water	18.02	-1.31	-1.31	Undiluted solution	-3.19	N.D.	34
Ethanol	46.08	-0.02	-1.31	Water	-3.50	N.D.	34
Mannitol	182.20	-2.89	-1.31	Water	-4.21	N.D.	34
Paraquat	186.28	-3.70	-1.31	Water	-5.06	N.D.	34
Methanol	32.05	-0.49	-1.31	Water	-3.09	N.D.	35
Ethanol	46.08	-0.02	-1.31	Water	-3.19	N.D.	35
Propanol	60.11	0.36	-1.31	Water	-2.69	N.D.	35
Butanol	74.14	0.84	-1.31	Water	-2.45	N.D.	35
Hexanol	102.20	1.94	-1.31	Water	-1.61	N.D.	35
Heptanol	116.23	2.49	-1.31	Water	-1.10	N.D.	35
Naproxen	230.28	3.36	-1.31	Water gel	-3.40	N.D.	36
Phenol	94.12	1.59	-1.31	pH 7.4 Buffer	-1.71	N.D.	37
Salicylic acid	138.13	1.57	-1.31	pH 7.4 Buffer	-3.48	N.D.	37
Naproxen	230.28	3.36	-1.31	pH 7.4 Buffer	-3.15	N.D.	37
Diclofenac	296.16	4.45	-1.31	pH 7.4 Buffer	-3.45	N.D.	37
Piroxicam	331.37	1.48	-1.31	pH 7.4 Buffer	-3.81	N.D.	37
Indomethacin	357.81	3.90	-1.31	pH 7.4 Buffer	-3.67	N.D.	37
Isoquinoline	129.17	1.84	-1.31	pH 5.0 Buffer	-1.78	N.D.	38
Salicylic acid	138.13	1.57	-1.31	pH 5.1 Buffer	-2.20	N.D.	38
Nicotine	162.26	1.34	-1.31	pH 5.2 Buffer	-1.71	N.D.	38
Barbitone	184.22	0.64	-1.31	pH 5.3 Buffer	-3.95	N.D.	38
Butobarbitone	212.28	1.72	-1.31	pH 5.4 Buffer	-3.71	N.D.	38
Amylobarbitone	226.31	2.24	-1.31	pH 5.5 Buffer	-2.64	N.D.	38
Phenobarbitone	232.26	1.49	-1.31	pH 5.6 Buffer	-3.34	N.D.	38
Hydrocortisone	362.51	1.73	-1.31	pH 5.7 Buffer	-3.93	N.D.	38
Sucrose	342.34	-3.21	-1.31	pH 4.0 Buffer	-5.28	N.D.	39
Hydrocortisone propinate	418.58	2.61	-1.31	pH 4.0 Buffer	-2.47	N.D.	39
Hydrocortisone hexanoate	460.67	3.48	-1.31	pH 4.0 Buffer	-1.74	N.D.	39
Hydrocortisone succinamate	461.61	1.29	-1.31	pH 4.0 Buffer	-4.59	N.D.	39
Hydrocortisone hemisuccinate	462.59	1.78	-1.31	pH 4.0 Buffer	-3.20	N.D.	39
Hydrocortisone methylsuccinate	476.62	2.17	-1.31	pH 4.0 Buffer	-3.68	N.D.	39
Hydrocortisone hydroxyhexanoate	476.67	2.56	-1.31	pH 4.0 Buffer	-3.04	N.D.	39
Hydrocortisone dimethylsuccinate	489.67	1.31	-1.31	pH 4.0 Buffer	-4.17	N.D.	39
Hydrocortisone octanoate	488.73	4.04	-1.31	pH 4.0 Buffer	-1.21	N.D.	39
Fluocinonide	494.58	2.86	-1.31	pH 4.0 Buffer	-2.77	N.D.	39
Hydrocortisone pimelamate	503.70	1.89	-1.31	pH 4.0 Buffer	-3.05	N.D.	39
Hydrocortisone hemipimelate	504.68	2.64	-1.31	pH 4.0 Buffer	-2.74	N.D.	39
Hydrocortisone methylpimelate	518.71	2.97	-1.31	pH 4.0 Buffer	-2.27	N.D.	39
Aniline	93.14	1.02	1.02	Undiluted solution	-2.73	N.D.	40
Aniline	93.14	1.04	-1.31	pH 7.4 Buffer	-1.66	N.D.	40
Benzaldehyde	106.13	1.49	1.49	Undiluted solution	-2.71	N.D.	40
Benzaldehyde	106.13	1.49	-1.31	pH 7.4 Buffer	-0.85	N.D.	40

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Anisole	108.15	1.99	1.99	Undiluted solution	-3.00	N.D.	40
Anisole	108.15	1.99	-1.31	pH 7.4 Buffer	-1.60	N.D.	40
2-Phenylethanol	122.18	1.55	1.55	Undiluted solution	-3.19	N.D.	40
2-Phenyl ethanol	122.18	1.62	-1.31	pH 7.4 Buffer	-1.42	N.D.	40
Benzyl alcohol	108.15	1.27	1.27	Undiluted solution	-3.27	N.D.	40
Benzyl alcohol	108.15	1.27	1.27	Undiluted solution	-3.28	N.D.	40
Benzyl alcohol	108.15	1.27	-1.31	pH 7.4 Buffer	-1.77	N.D.	40
Benzyl alcohol	108.15	1.27	0.75	Propylene carbonate : Benzyl alcohol = 50 : 50	-3.51	N.D.	40
Benzyl alcohol	108.15	1.27	1.42	Butyl acetate : Benzyl alcohol = 50 : 50	-3.34	N.D.	40
Benzyl alcohol	108.15	1.27	1.73	Isophorone : Benzyl alcohol = 50 : 50	-3.44	N.D.	40
Benzyl alcohol	108.15	1.27	3.95	*n*-Heptane : Benzyl alcohol = 92 : 8	-1.24	N.D.	40
Benzyl alcohol	108.15	1.27	0.95	Butanol : Benzyl alcohol = 74 : 26	-3.26	N.D.	40
Benzyl alcohol	108.15	1.27	0.97	Butanol : Benzyl alcohol = 69 : 31	-3.19	N.D.	40
Benzyl alcohol	108.15	1.27	1.06	Butanol : Benzyl alcohol = 50 : 50	-3.33	N.D.	40
Benzyl alcohol	108.15	1.27	1.10	Butanol : Benzyl alcohol = 40 : 60	-3.06	N.D.	40
Benzyl alcohol	108.15	1.27	1.19	Butanol : Benzyl alcohol = 18 : 82	-3.34	N.D.	40
Benzyl alcohol	108.15	1.27	1.52	Toluene : Benzyl alcohol = 19 : 81	-2.92	N.D.	40
Benzyl alcohol	108.15	1.27	1.64	Toluene : Benzyl alcohol = 29 : 71	-2.66	N.D.	40
Benzyl alcohol	108.15	1.27	1.92	Toluene : Benzyl alcohol = 50 : 50	-2.51	N.D.	40
Benzyl alcohol	108.15	1.27	2.06	Toluene : Benzyl alcohol = 61 : 39	-2.35	N.D.	40
Benzyl alcohol	108.15	1.27	2.30	Toluene : Benzyl alcohol = 79 : 21	-1.98	N.D.	40
Benzyl alcohol	108.15	1.27	2.31	Isopropyl myristate : Benzyl alcohol = 16 : 84	-2.56	N.D.	40
Benzyl alcohol	108.15	1.27	3.18	Isopropyl myristate : Benzyl alcohol = 30 : 70	-2.70	N.D.	40
Benzyl alcohol	108.15	1.27	4.44	Isopropyl myristate : Benzyl alcohol = 50 : 50	-2.79	N.D.	40
Benzyl alcohol	108.15	1.27	5.90	Isopropyl myristate : Benzyl alcohol = 73 : 27	-2.35	N.D.	40
Benzyl alcohol	108.15	1.27	6.86	Isopropyl myristate : Benzyl alcohol = 88 : 12	-2.42	N.D.	40
Butanol	74.14	0.84	-1.31	PBS	-2.66	N.D.	41
Benzene	78.12	2.09	-1.31	PBS	-0.80	N.D.	41
Caffeine	194.22	-0.36	-1.31	PBS	-4.00	N.D.	41
Estradiol	272.42	3.83	-1.31	PBS	-2.49	N.D.	41
Testosterone	288.47	3.43	-1.31	PBS	-2.66	N.D.	41
Progesterone	314.51	3.29	-1.31	PBS	-1.89	N.D.	41
Corticosterone	346.51	2.45	-1.31	PBS	-3.52	N.D.	41
Theophylline	180.19	-0.71	1.02	Propionic acid : Diethylen glycol lauryl ether = 80 : 20	-1.56	N.D.	42
Adenosine	267.28	-1.56	1.02	Propionic acid : Diethylen glycol lauryl ether = 80 : 20	-1.71	N.D.	42
Isopropyl alcohol	60.11	0.47	0.47	Undiluted solution	-2.55	N.D.	43
Physostigmine	275.39	2.27	0.47	Isopropyl alcohol	-4.05	N.D.	43
Physostigmine	275.39	2.27	7.61	Isopropyl myristate	-2.81	N.D.	43
Isopropyl alcohol	60.11	0.47	6.90	Isopropyl alcohol : Isopropyl myristate = 10 : 90	-1.64	N.D.	43
Physostigmine	275.39	2.27	6.90	Isopropyl alcohol : Isopropyl myristate = 10 : 90	-2.63	N.D.	43
Isopropyl alcohol	60.11	0.47	4.04	Isopropyl alcohol : Isopropyl myristate = 50 : 50	-1.35	N.D.	43
Physostigmine	275.39	2.27	4.04	Isopropyl alcohol : Isopropyl myristate = 50 : 50	-3.08	N.D.	43
Isopropyl alcohol	60.11	0.47	2.61	Isopropyl alcohol : Isopropyl myristate = 70 : 30	-1.81	N.D.	43
Physostigmine	275.39	2.27	2.61	Isopropyl alcohol : Isopropyl myristate = 70 : 30	-3.32	N.D.	43

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Isopropyl alcohol	60.11	0.47	1.18	Isopropyl alcohol : Isopropyl myristate = 90 : 10	-2.21	N.D.	43
Physostigmine	275.39	2.27	1.18	Isopropyl alcohol : Isopropyl myristate = 90 : 10	-3.79	N.D.	43
Isopropyl alcohol	60.11	0.47	5.47	Isopropyl alcohol : Isopropyl myristate = 30 : 70	-1.51	N.D.	43
Physostigmine	275.39	2.27	5.47	Isopropyl alcohol : Isopropyl myristate = 30 : 70	-2.84	N.D.	43
Dimethyl phthalate	194.20	1.43	-0.71	Propylene glycol	-3.60	N.D.	44
Dimethyl phthalate	194.20	1.43	3.02	Octanol	-3.85	N.D.	44
Dimethyl phthalate	194.20	1.43	4.95	Ethyl decanoate	-3.60	N.D.	44
Fluazifop-*p*-butyl	383.40	4.96	-0.71	Propylene glycol	-4.41	N.D.	44
Fluazifop-*p*-butyl	383.40	4.96	3.02	Octanol	-5.00	N.D.	44
Fluazifop-*p*-butyl	383.40	4.96	4.95	Ethyl decanoate	-5.19	N.D.	44
Fomesafen sodium	461.77	2.87	-0.71	Propylene glycol	-5.68	N.D.	44
Fomesafen sodium	461.77	2.87	3.02	Octanol	-4.24	N.D.	44
Fomesafen sodium	461.77	2.87	4.95	Ethyl decanoate	-2.68	N.D.	44
Baclofen	227.71	0.63	-1.31	Water	-4.41	N.D.	45
Baclofen	227.71	0.63	-0.08	Ethanol : Water = 95 : 5	-3.46	N.D.	45
Caffeine	194.22	-0.36	-1.31	Water gel	-3.29	N.D.	46
Caffeine	194.22	-0.36	-1.39	Ethylene glycol gel	-3.68	N.D.	46
Testosterone	288.47	3.43	-1.31	Water gel	-2.17	N.D.	46
Testosterone	288.47	3.43	-1.39	Ethylene glycol gel	-3.74	N.D.	46
Propionic acid	74.09	0.12	0.12	Undiluted solution	-1.52	N.D.	47
Hexanoic acid	116.18	1.44	1.44	Undiluted solution	-2.74	N.D.	47
Octanoic acid	144.24	2.31	2.31	Undiluted solution	-3.38	N.D.	47
Theophylline	180.19	-0.71	0.12	Propionic acid	-1.90	N.D.	47
Theophylline	180.19	-0.71	1.44	Hexanoic acid	-1.76	N.D.	47
Theophylline	180.19	-0.71	2.31	Octanoic acid	-1.60	N.D.	47
Theophylline	180.19	-0.71	0.78	Propionic acid : Hexanoic acid = 50 : 50	-1.52	N.D.	47
Theophylline	180.19	-0.71	1.22	Propionic acid : Octanoic acid = 50 : 50	-1.38	N.D.	47
Theophylline	180.19	-0.71	1.88	Hexanoic acid : Octanoic acid = 50 : 50	-1.70	N.D.	47
Theophylline	180.19	-0.71	2.21	Propionic acid : Lauric acid = 50 : 50	-1.19	N.D.	47
Adenosine	267.28	-1.56	1.44	Hexanoic acid	-2.02	N.D.	48
Adenosine	267.28	-1.56	0.12	Propionic acid	-2.14	N.D.	48
Adenosine	267.28	-1.56	1.18	Propionic acid : Hexanoic acid = 20 : 80	-1.88	N.D.	48
Adenosine	267.28	-1.56	0.91	Propionic acid : Hexanoic acid = 40 : 60	-1.62	N.D.	48
Adenosine	267.28	-1.56	0.65	Propionic acid : Hexanoic acid = 60 : 40	-1.63	N.D.	48
Adenosine	267.28	-1.56	3.87	Propionic acid : Isopropyl myristate = 50 : 50	-1.45	N.D.	48
Adenosine	267.28	-1.56	1.99	Propionic acid : Isopropyl myristate = 75 : 25	-1.47	N.D.	48
Adenosine	267.28	-1.56	1.24	Propionic acid : Isopropyl myristate = 85 : 15	-1.68	N.D.	48
Adenosine	267.28	-1.56	0.57	Propionic acid : Isopropyl myristate = 94 : 6	-1.92	N.D.	48
Adenosine	267.28	-1.56	0.67	Propionic acid : Octanoic acid = 75 : 25	-1.51	N.D.	48
Salicylic acid	138.13	1.57	-0.25	Ethanol : Propylene glycol = 67 : 33	-3.05	N.D.	49
Ketorolac acid	259.33	1.02	0.50	Ethanol : Propylene glycol : Isopropyl myristate = 55 : 35 : 10	-2.73	N.D.	50
Ketorolac acid	259.33	1.02	0.17	Isopropyl alcohol : Water : Isopropyl myristate = 58 : 37 : 5	-2.59	N.D.	50
Ketorolac acid	259.33	1.02	6.38	Isopropyl myristate : Glycerol monocaprylate = 80 : 20	-2.77	N.D.	50
Benzoic acid	122.13	1.54	-0.71	Propylene glycol	-2.66	N.D.	51

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
5-Fluorouracil	130.09	-0.79	-0.71	Propylene glycol	-3.96	N.D.	51
Testosterone	288.47	3.43	-0.71	Propylene glycol	-4.23	N.D.	51
Naloxone	327.41	0.88	-0.71	Propylene glycol	-3.89	N.D.	51
Indomethacin	357.81	3.90	-0.71	Propylene glycol	-4.18	N.D.	51
Methotrexate	454.50	-1.70	-0.71	Propylene glycol	-2.59	N.D.	51
5-Fluorouracil	130.09	-0.79	-0.71	Propylene glycol	-3.60	N.D.	52
5-Fluorouracil	130.09	-0.79	-1.31	Saline	-4.02	N.D.	52
2-Phenoxyethanol	138.18	1.19	-0.49	Methanol	-2.87	N.D.	53
Sodium lauryl sulphate	288.42	2.73	-1.31	Water	-2.54	N.D.	54
Retinoic acid	300.48	5.90	-0.02	Ethanol	-3.85	N.D.	54
Anthralin	206.25	2.64	1.69	Chloroform	-4.63	N.D.	55
Ketorolac acid	259.33	1.02	-1.31	Water	-2.24	N.D.	56
Ketorolac acid	259.33	1.02	-0.95	Isopropyl alcohol : Water : Isopropyl myristate = 20 : 80 : 0.1	-1.69	N.D.	56
Ketorolac acid	259.33	1.02	-0.76	Isopropyl alcohol : Water : Isopropyl myristate = 30 : 70 : 0.2	-2.14	N.D.	56
Ketorolac acid	259.33	1.02	-0.57	Isopropyl alcohol : Water : Isopropyl myristate = 40 : 60 : 0.3	-2.38	N.D.	56
Ketorolac acid	259.33	1.02	-0.31	Isopropyl alcohol : Water : Isopropyl myristate = 50 : 50 : 1.4	-2.55	N.D.	56
Ketorolac acid	259.33	1.02	-0.30	Isopropyl alcohol : Water : Isopropyl myristate = 50 : 50 : 1.5	-2.47	N.D.	56
Ketorolac acid	259.33	1.02	-0.09	Isopropyl alcohol : Water : Isopropyl myristate = 60 : 40 : 2	-2.55	N.D.	56
Ketorolac acid	259.33	1.02	-0.95	Isopropyl alcohol : Water = 20 : 80	-2.09	N.D.	56
Ketorolac acid	259.33	1.02	-0.78	Isopropyl alcohol : Water = 30 : 70	-2.50	N.D.	56
Ketorolac acid	259.33	1.02	-0.60	Isopropyl alcohol : Water = 40 : 60	-2.85	N.D.	56
Ketorolac acid	259.33	1.02	-0.42	Isopropyl alcohol : Water = 50 : 50	-3.10	N.D.	56
Ketorolac acid	259.33	1.02	-0.24	Isopropyl alcohol : Water = 60 : 40	-3.19	N.D.	56
Ketorolac acid	259.33	1.02	0.11	Isopropyl alcohol : Water = 80 : 20	-3.50	N.D.	56
Ketorolac acid	259.33	1.02	0.47	Isopropyl alcohol	-3.90	N.D.	56
Water	18.02	-1.31	-1.31	Undiluted solution	-2.57	N.D.	57
Water	18.02	-1.31	-0.67	Ethanol : Water = 50 : 50	-2.44	N.D.	57
Ethanol	46.08	-0.02	-0.67	Ethanol : Water = 50 : 50	-2.72	N.D.	57
5-Fluorouracil	130.09	-0.79	-1.31	Water	-4.51	N.D.	58
5-Fluorouracil	130.09	-0.79	-1.19	Water : Propylene glycol = 80 : 20	-4.46	N.D.	58
5-Fluorouracil	130.09	-0.79	-1.01	Water : Propylene glycol = 50 : 50	-4.45	N.D.	58
5-Fluorouracil	130.09	-0.79	-0.83	Water : Propylene glycol = 20 : 80	-4.37	N.D.	58
Vanillylnonanamide	293.45	3.92	-0.71	Propylene glycol	-4.73	N.D.	59
Octadec-9-enoic acid 4-(2-aminoethoxy)-3-methoxybenzylamide	460.78	7.56	-0.71	Propylene glycol	-6.48	N.D.	59
Olvanil	417.70	7.88	-0.71	Propylene glycol	-4.85	N.D.	59
Water	18.02	-1.31	-1.31	Undiluted solution	-2.81	N.D.	60
Water	18.02	-1.31	-1.31	Undiluted solution	-2.81	N.D.	60
Ethanol	46.08	-0.02	-1.31	Water	-3.22	N.D.	61, 62
Heptanol	116.23	2.49	-1.31	Water	-1.46	N.D.	61, 62
Ethanol	46.08	-0.02	7.61	Isopropyl myristate	-2.02	N.D.	61, 62
Heptanol	116.23	2.49	7.61	Isopropyl myristate	-3.70	N.D.	61, 62
Water	18.02	-1.31	-1.31	Undiluted solution	-2.77	N.D.	63
Cortisone	360.49	2.08	-1.31	Water	-4.48	N.D.	64

Table 1. (Continued)

Chemical name	Values by Pallas analysis			Reported data and reference			
	MW_c	Log P_c	Log P_v	Vehicle	Log K_p (cm/hr)	Log D (cm^2/hr)	Reference number
Cortisone	360.49	2.08	0.30	Acetone	-3.77	N.D.	64
Triprolidine monohydrate	296.45	3.50	-0.71	Propylene glycol	-4.02	N.D.	65
Triprolidine monohydrate	296.45	3.50	5.08	Diisopropyl sebacate	-4.01	N.D.	65
Triprolidine monohydrate	296.45	3.50	7.61	Isopropyl myristate	-3.84	N.D.	65
2-Ethoxyethanol	90.14	-0.18	-0.18	Undiluted solution	-4.13	N.D.	66
2-Ethoxyethanol	90.14	-0.18	-0.49	Methanol	-4.23	N.D.	66
Estradiol	272.42	3.83	-1.31	Water	-2.21	N.D.	67
Estradiol	272.42	3.83	-0.99	Ethanol : Water = 25 : 75	-2.28	N.D.	67
Estradiol	272.42	3.83	-0.34	Ethanol : Water = 75 : 25	-3.10	N.D.	67
Estradiol	272.42	3.83	-0.08	Ethanol : Water = 95 : 5	-2.91	N.D.	67

References 1; Scheuplein and Blank (1973), 2; Roberts *et al.* (1977), 3; Singh *et al.* (1995), 4; Scheuplein *et al.* (1969), 5; Blank *et al.* (1967), 6; Scheuplein and Blank (1971), 7; Vaddi *et al.* (2001), 8; Pongjanyakul *et al.* (2002), 9; Roy and Flynn (1989), 10; Roy and Flynn (1990), 11; Jolicoeur *et al.* (1992), 12; Dugard and Scott (1986), 13; Blank and McAuliffe (1985), 14; Ross and Shah (2000), 15; Roy and Manoukian (1994), 16; Pershing *et al.* (1993), 17; Jenner *et al.* (1995), 18; Vaddi *et al.* (2003), 19; Walters *et al.* (1997), 20; Tenjarla *et al.* (1996), 21; Koch *et al.* (1987), 22; Barber *et al.* (1992), 23; Michaels *et al.* (1975), 24; Bond and Barry (1988b), 25; Bronaugh and Congdon (1984), 26; Jacques *et al.* (1987), 27; Cross *et al.* (2003), 28; Anigbogu *et al.* (1996), 29; Scott and Rhodes (1988), 30; Cordero *et al.* (1997), 31; Galey *et al.* (1976), 32; Dolezal *et al.* (1993), 33; Díez Sales *et al.* (1993), 34; Scott *et al.* (1991), 35; McAuliffe and Blank (1991), 36; Chowhan and Pritchard (1978), 37; Singh and Roberts (1994), 38; Hadgraft and Ridout (1987), 39; Anderson *et al.* (1988), 40; Barry *et al.* (1985), 41; Mitragotri *et al.* (1995), 42; Kadir *et al.* (1989), 43; Pardo *et al.* (1990), 44; Hilton *et al.* (1994), 45; Sznitowska *et al.* (1998), 46; Bronaugh and Franz (1986), 47; Kadir *et al.* (1987), 48; Kadir *et al.* (1988), 49; Megwa *et al.* (2000), 50; Roy *et al.* (1995), 51; Aungst *et al.* (1990), 52; Bond and Barry (1988a), 53; Roper *et al.* (1997), 54; Effendy *et al.* (1996), 55; Schalla *et al.* (1981), 56; Roy and Manoukian (1995), 57; Magnusson *et al.* (1997), 58; Yamane *et al.* (1995), 59; Kasting *et al.* (1997), 60; Bronaugh *et al.* (1986), 61; Idson (1975), 62; Scheuplein (1965), 63; Harrison *et al.* (1984), 64; Scheuplein and Ross (1974), 65; Kasting *et al.* (1993), 66; Lockley *et al.* (2002), 67; Knutson *et al.* (1993).
N.D.; Not done, PBS; Phosphate buffered saline.

using QwikNet Ver.2.23 (http://www.kagi.com/cjensen.).

For the prediction of log K_p, the input layer consisted of three descriptors, *i.e.*, MW_c, log P_c and log P_v, while the output layer contained log K_p as the response variable. The hidden layer was positioned between the input layer and the output layer, and contained five units.

For the prediction of log D, the input layer consisted of two molecular descriptor variables, *i.e.*, the MW_c and Log P_c, while the output layer contained log D as the response variable. The hidden layer contained five units.

The log K_p or log D values were associated with descriptors by training the ANN system. The range of weights was set to be -6 to 6 for log K_p and -5 to 5 for log D. Gaussian noise at the 5% level was added to the input patterns in back-propagation training in order to avoid "overfitting" of the data (Holmstrom and Koistinen, 1992). The model was also validated by means of a 10-fold cross validation procedure.

Statistical analysis

The correlation coefficient (r value) was determined by means of Pearson's correlation statistics. Multiple linear regression (MLR) analysis using the forward selection method was performed by Excel Statistics 2002 software (Social Survey Research Information, Tokyo, Japan).

Calculation of the *Q*24hr

The value of Q24hr, the cumulative amount of chemical permeated into the skin during 24 hr, was calculated from the obtained K_p and D by applying Fick's law of diffusion, according to the following equation:

$$Q24hr = K_p \times C_o \times [24 - h^2/(6 \times D)]$$

Where C_o is concentration of chemicals and h is the thickness of skin (estimated as 20 μm).

RESULTS

Physicochemical properties of chemicals listed

Table 1 summarizes the values of MW_c and log P_c of 359 chemicals, as well as log P_v of the vehicles used. The values of log K_p and log D from the literature or obtained by calculation from literature data were in the ranges of -6.98 to -0.80 and -8.76 to -4.06, respectively. The reported values of MW_c, log P_c and log P_v were in the ranges of 18.02 to 765.05, -3.70 to 7.88 and -1.39 to 8.72, respectively. These values cover a wide range of physicochemical properties.

Prediction of log K_p and log D by MLR analysis

For MLR analyses of log K_p and log D, the following equations were obtained (see Materials and Methods):

For log K_p,

$$\log K_p = -0.193 \times \log P_c \times \log P_v + 0.00124 \times MW_c \times \log P_v - 0.00476 \times MW_c + 0.0184 \times \mathrm{Log}\, P_v^2 + 0.00000352 \times MW_c^2 - 2.23$$

$n = 359$, $r^2 = 0.423$, $F = 51.7$, RMS error = 0.887, CV RMS error = 0.914

RMS error rate of increase = 1.04

For log D,

$$\log D = -0.0228 \times MW_c + 0.0000332 \times MW_c^2 + 0.185 \times \log P_c + 0.0435 \times \mathrm{Log}\, P_c^2 - 4.29$$

$n = 107$, $r^2 = 0.681$, $F = 54.4$, RMS error = 0.658, CV RMS error = 0.708

RMS error rate of increase = 1.08

Where n is the number of data points, r^2 is the squared correlation coefficient between observed and predicted log K_p, F is the critical value in F-statistics, the RMS error is root-mean-square error of the prediction and the RMS error rate of increase is the ratio of predicted value after cross-validation to that before.

Prediction of log K_p by ANN analysis

Fig. 1 shows the relationship between observed and calculated log K_p obtained by MLR (Fig. 1(A)) and by ANN (Fig. 1(B)) analyses of 359 chemicals. The RMS error obtained for ANN was 0.675, which is smaller than that for MLR (0.887). Fig. 2 shows the results of 10-fold cross-validation for log K_p by ANN analysis. The relationship between observed and predicted log K_p was analyzed using the chemicals listed in Table 1. The predictive RMS error for the 10-fold cross-validation analysis was 0.723. In the comparison between observed and predicted log K_p, the MLR analysis showed 98 and 8 samples with a disparity of more than ten and more than one hundred times, respectively, while the ANN analysis showed 62 and 3 samples with a disparity of more than ten and more than one hundred times, respectively. Thus, the ANN model was able to predict skin permeability with higher accuracy.

Prediction of log D by ANN analysis

Fig. 3 shows the relationship between observed and predicted log D obtained by MLR (Fig. 3(A)) and ANN (Fig. 3(B)) analyses of 107 chemicals. The RMS error obtained for ANN was 0.553, which was smaller than that for the MLR (0.658). Fig. 4 shows the results of 10-fold

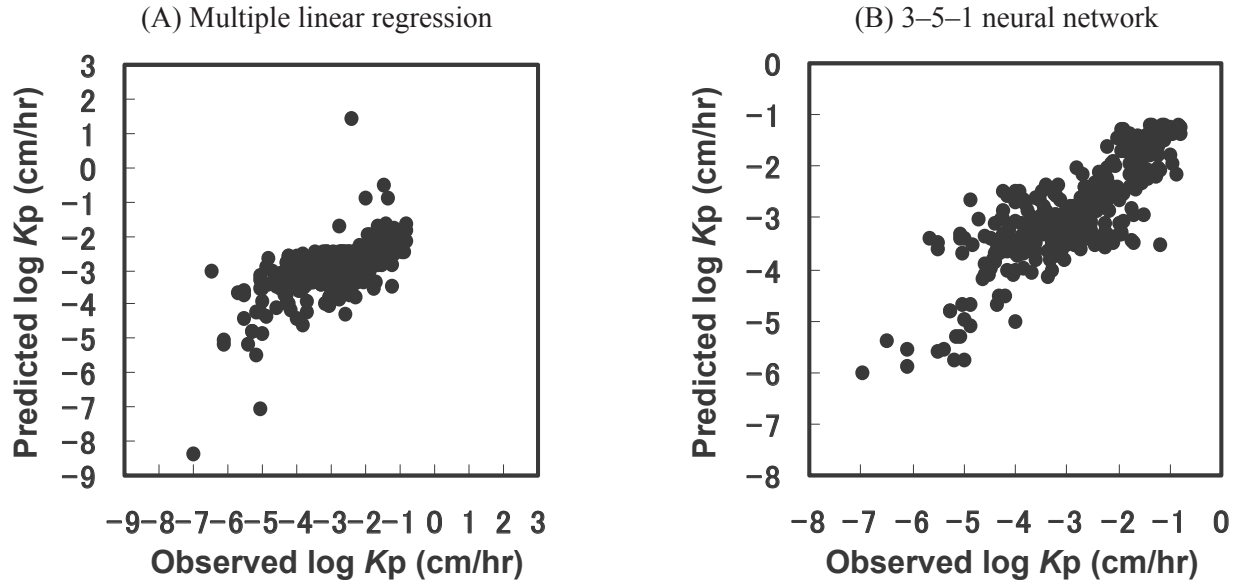

Fig. 1. Relationship between experimental and calculated skin permeability coefficients. Plots (A) and (B) were obtained from the analyses using multiple linear regression and the 3-5-1 neural network, respectively. The line represents 1-to-1 correspondence.

cross-validation for log *D* by ANN analysis. The relationship between observed and predicted log *D* was analyzed using the chemicals listed in Table 2. The predictive RMS error for the 10-fold cross-validation analysis was 0.606. In the comparison between observed and predicted log *D*, the MLR analysis showed 18 and 1 samples with a disparity of more than ten and one hundred times, respectively, while the ANN analysis showed 10 and 1 samples with a disparity of more than ten and more than one hundred times, respectively. Therefore, the ANN model could predict apparent diffusion in the skin with higher accuracy.

Effect of vehicle on prediction of permeated amounts of chemicals

Fig. 5 shows the predicted *Q*24hr of 359 chemicals in water and ester oil vehicles. The *Q*24hr values of these chemicals fell in a broad range when water was used as the vehicle, but a much narrower range when ester oil was used as the vehicle. Benzene exemplifies the difference between *Q*24hr values in water and ester oil.

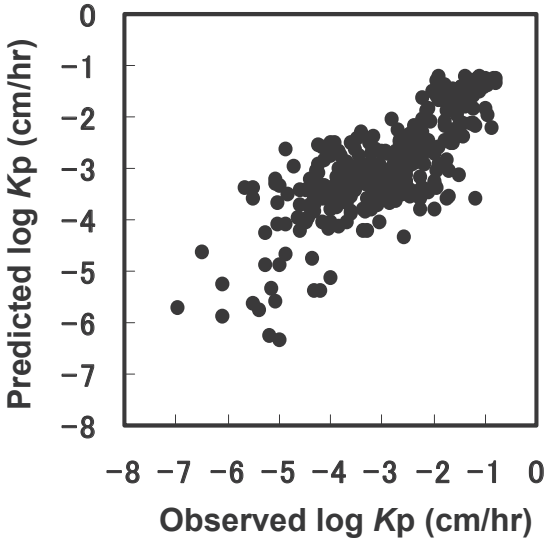

Fig. 2. Leave-some-out cross-validation of 3-5-1 neural network for prediction of skin permeability coefficient.

DISCUSSION

Percutaneous absorption involves partitioning and diffusion processes that are influenced in various ways by physicochemical factors, such as molecular weight and log *P* of the chemical. The main factors that affect the partitioning process are the relationship among chemical, vehicle and skin. For example, since the stratum corneum is lipophilic in nature, oil-soluble chemicals have a higher affinity for the stratum corneum than do water-soluble chemicals. On the other hand, a chemical that has high-

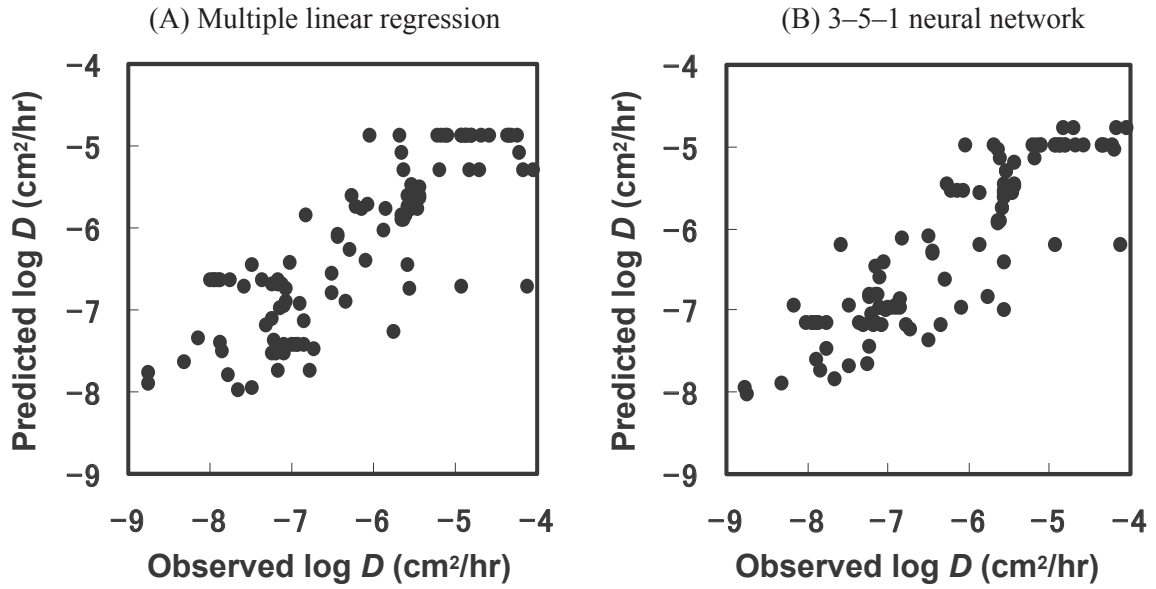

Fig. 3. Relationship between experimental and calculated apparent diffusion coefficients. Plots (A) and (B) were obtained from the analyses using multiple linear regression and the 2-5-1 neural network, respectively. The line represents 1-to-1 correspondence.

er solubility will be retained more in the vehicle, and this decreases the magnitude of partitioning. The diffusibility of a chemical is also important, because large molecular size leads to decreased diffusibility, thereby decreasing the magnitude of percutaneous absorbability. Thus, the magnitude of percutaneous absorbability of chemicals markedly depends upon the balance of affinity between compound and vehicle and between compound and stratum corneum, and also upon the molecular size of the compound (Dugard and Scott, 1986).

Here, in order to develop an ANN model for prediction of percutaneous absorption of chemicals, we first created a dataset of reported *Kp* and *D* values. The database contained 359 records, consisting of combinations of 149 chemicals and 121 simple or blended vehicles. The quality (*i.e.*, reliability), scale and structural range of a dataset all influence *in silico* prediction, so we included structurally diverse chemicals in the database. Our ANN model could predict well in the dataset ranges. However, it should be noted that our method is not applicable to chemicals of unknown or poorly defined molecular weight, such as proteins and polymers, or natural materials consisting of multiple components, such as herbal extracts.

Ghafourian *et al.* (2010) developed a model for predicting skin penetration by multiple linear regression analysis, using a dataset of 384 samples. However, the dataset consisted of combinations of only 16 chemicals and

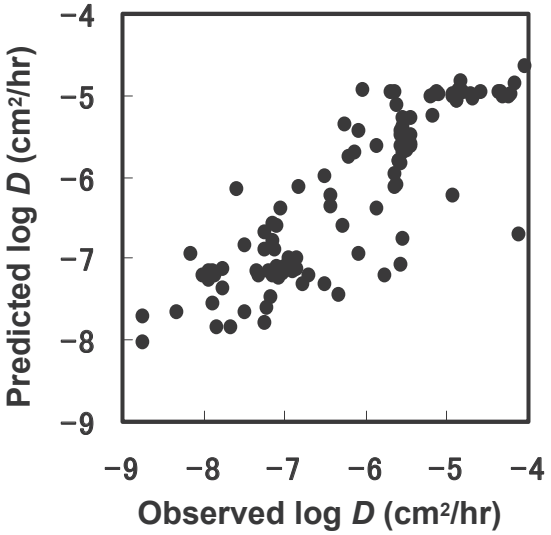

Fig. 4. Leave-some-out cross-validation of 2-5-1 neural network for prediction of apparent diffusion coefficient.

24 simple or blended vehicles. With our dataset, we found that ANN analysis was superior to multiple linear regression analysis. One possible reason for this is that datasets of compounds with a broader range of chemical properties tend to result in a better correlation in ANN analysis, whereas multiple linear regression analysis tends to give

Table 2. Architecture of MLR and ANN.

Parameter	N	Descriptor	MLR			ANN			
			R^2	RMS error	CV RMS error	Model	R^2	RMS error	CV RMS error
K_p	359	MW_c, logP_c, logP_v	0.423	0.887	0.914	3-5-1	0.666	0.675	0.723
D	107	MW_c, logP_c	0.681	0.658	0.708	2-5-1	0.779	0.553	0.606

N is the number of data points, R^2 is the squared correlation coefficient between observed and predicted log K_p or log D for the test sets, and RMS error is the root-mean-square error of prediction.

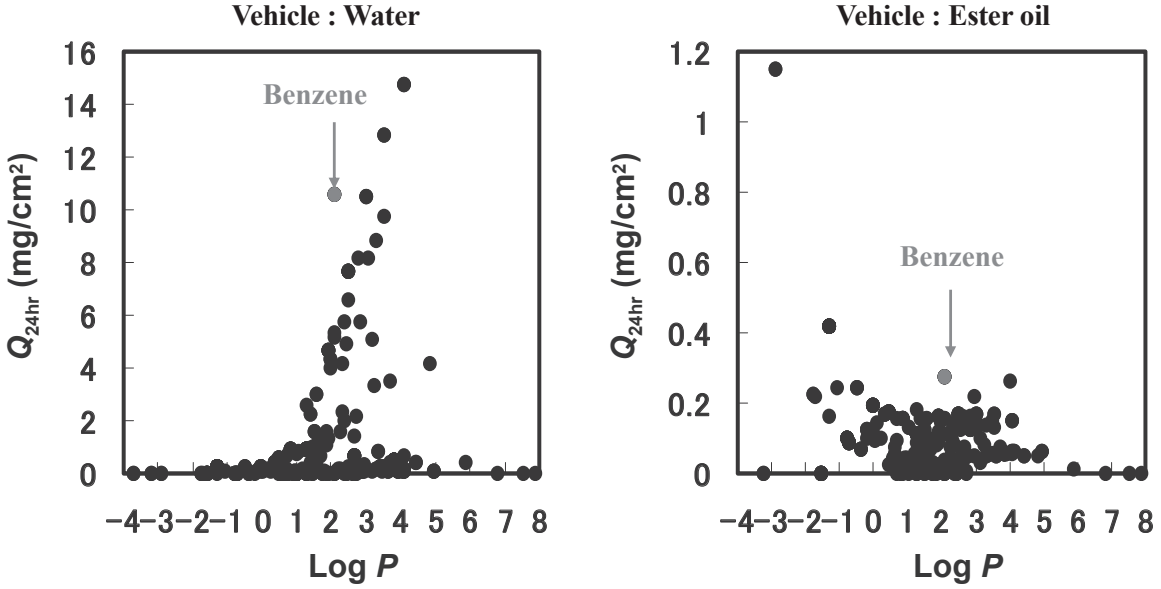

Fig. 5. Effects of log P and vehicle on prediction of permeated amounts of chemicals.
$Q_{24hr} = K_p \times C_0 \times [(24 - h^2/(6 \times D)]$
Q_{24hr} : Permeated amounts of chemicals during 24 hr
C_0: Concentration of chemicals in the vehicle (1%)
h : Thickness of the skin (20 μm)

a better correlation with datasets of compounds having a relatively restricted range of properties.

We adopted log P_c and MW_c, which are simple, widely used molecular descriptors that were employed by Potts and Guy (1992) to predict skin permeability of a large number of structurally diverse compounds. These descriptors are straightforward and have clear physical significance in comparison with the complex descriptors used in other studies; for example, Lim *et al.* (2002) used molecular orbital calculation, Ghafourian *et al.* (2010) used rather complicated physicochemical properties, Pugh *et al.* (2000) used H-bonding and electronic charge, Naegel *et al.* (2008) used a geometric mathematical modeling, and Rim *et al.* (2009) used molecular dynamics simulations of diffusion.

A feature of the present model is the introduction of log P_v as a molecular descriptor. Since log K_p is influenced by the vehicle, a descriptor characterizing the nature of the vehicle is clearly needed. Ghafourian *et al.* (2010) used the boiling point and the Hildebrand solubility parameter of the vehicle, but they focused on porcine skin permeability, because porcine skin morphologically resembles human skin. However, risk assessment of chemicals is required to predict their permeation in human skin, so we considered that it would naturally be better to focus directly on human skin. Prediction based on physicochemical properties of chemicals, such as MW_c and log P_c, has been questioned based on the fact that they give little information as to the actual structural features of solutes that influence skin permeability (Dugard and Scott, 1986). Instead, we considered that log P_v would be an effective descriptor of affinity and overall structural features, and

would also improve the prediction of log K_p. Further, the selection of log K_p and log D as parameters allows us to calculate the cumulative amount of chemical permeated into the skin during 24 hr from the predicted values by applying Fick's law of diffusion.

The predictability of log K_p and log D by the ANN analysis was superior to that by the MLR analysis (Table 2), and we used the values predicted by the ANN analysis to calculate Q24hr. As shown in Fig. 5, the calculated Q24hr values appeared to reflect well the fact that stratum corneum is lipophilic, while epidermis is hydrophilic. Thus, when water is used as a vehicle, chemicals having log P of 2 to 4 moderately lipophilic show high values of Q24hr because of their moderate permeability into both stratum corneum and epidermis. In addition, as exemplified by benzene, Q24hr of an individual chemicals depends markedly upon the vehicle used. On the other hand, freely water-soluble chemicals that have log P of less than 2 show low values of the Q24hr because the stratum corneum behaves as a barrier, while slightly water-soluble chemicals that have a log P of more than 4 also show low values of Q24hr because the epidermis behaves as a barrier. Thus, the relationship between log P and the Q24hr of the chemicals is bell-shaped, if the vehicle is water, whereas this is not the case when the vehicle is ester oil. Consequently, the nature of the relationship between log P and the Q24hr of the chemicals depends upon the characteristics of the vehicle, as would intuitively be expected.

In conclusion, our ANN-based prediction system for log K_p and log D, using MW_c, log P_c and log P_v as input parameters, appears to be effective for calculation of the Q24hr. If NOAEL data are available from repeated-dose oral toxicity studies, the calculated value of Q24hr enables calculation of the MoS, which is a key requirement for risk assessment of cosmetic ingredients.

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Conflict of interest---- The authors declare that there is no conflict of interest.

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