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An *in silico* skin absorption model for fragrance materials

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ABSTRACT

Fragrance materials are widely used in cosmetics and other consumer products. The Research Institute for Fragrance Materials (RIFM) evaluates the safety of these ingredients and skin absorption is an important parameter in refining systemic exposure. Currently, RIFM's safety assessment process assumes 100% skin absorption when experimental data are lacking. This 100% absorption default is not supportable and alternate default values were proposed. This study aims to develop and validate a practical skin absorption model (SAM) specific for fragrance material. It estimates skin absorption based on the methodology proposed by Kroes et al. SAM uses three default absorption values based on the maximum flux (J_{max}) – namely, 10%, 40%, and 80%. J_{max} may be calculated by using QSAR models that determine octanol/water partition coefficient (K_{ow}), water solubility (S) and permeability coefficient (K_p). Each of these QSAR models was refined and a semi-quantitative mechanistic model workflow is presented. SAM was validated with a large fragrance-focused data set containing 131 materials. All resulted in predicted values fitting the three-tiered absorption scenario based on J_{max} ranges. This conservative SAM may be applied when fragrance material lack skin absorption data.

1. Introduction

Skin absorption is a very important parameter for safety assessment, especially for topically applied fragrance materials. Chemicals in contact with the skin have the potential to be absorbed into the skin and enter the systemic circulation. To enter the systemic circulation, the chemical must reach the underlying dermis replete with capillaries. Skin absorption occurs by passive diffusion through the epidermis and directly by sweat glands and hair follicles (Ngo et al., 2010). Chemicals that penetrate no further than the epidermis are destined to be eliminated by desquamation and thus not reach the systemic circulation (Sundberg et al., 2012). Therefore, determining the penetration of a substance is crucial for assessing systemic exposure.

Usually, skin absorption of a target material is obtained experimentally *in vitro* and/or *in vivo* based on different species, including pig, monkey and human subjects. In the absence of experimental skin absorption data, it is customary, by safety assessors, to extrapolate via read-across structural analogs or use default values. The European Commission (EC) guidance on dermal absorption, proposed two default values – 100% or 10% if the substance of interest is very lipophilic or very hydrophilic (i.e., **log** K_{ow} <–1 or >+4) with a MW >500 (European Commission, 2004). For pesticides, the European Food Safety Authority (EFSA) replaced these EC default values with 25% for liquid concentrates and 75% when diluting them for spraying (EFSA Panel on Plant Protection Products and their Residues, 2011, 2012). More recently however, Aggarwal et al. (2014) analyzed human skin absorption data on pesticides that were available until 2012 and proposed a 6% default value for liquid concentrates and 30% for spray dilutions.

Currently, in RIFM's (Research Institute for Fragrance Materials) safety assessment process, a 100% default absorption value is applied for materials without experimental data (Belsito et al., 2007, 2011, 2012a, 2012b, 2012c). However, as discussed by Kroes et al. (2007), "the assumption of 100% absorption is not scientifically supportable" and, based on their analysis of 15 cosmetic ingredients and 62 chemicals in the EDETOX database (Williams, 2004), they proposed three default skin absorption values for cosmetic ingredients. Based on their derivation and analysis, the three different default skin absorption values proposed were based on the maximum flux (J_{max}, in unit of μg/cm^2/h). J_{max} is the theoretically achieved dose, based on Fick's first law of diffusion (Fick, 1855), when a material

Abbreviations: RIFM, Research Institute for Fragrance Materials; SAM, skin absorption model; QSAR, Quantitative Structure–Activity Relationship; EC, European Commission; EFSA, European Food Safety Authority; EDETOX, Evaluations and Predictions of Dermal Absorption of Toxic Chemicals; USEPA, United States Environmental Protection Agency; ACTOR, Aggregated Computational Toxicology Resource; SE, standard error; OECD, Organisation for Economic Co-operation and Development; RMSE, root-mean-square deviation; TTC, Threshold of Toxicological Concern; MOE, margin of exposure; MOS, margin of safety; CAESAR, Computer Assisted Evaluation of industry chemical Substances According to Regulations.

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is maintained in a saturated solution or at steady state equilibrium whose flux describes the amount of permeant per unit time and area (i.e., μg/cm²/h) (Magnusson et al., 2004). J_{max} is independent of the formulation in which the material contacts the skin and is a constant value when the formulation does not change the skin barrier (Kroes et al., 2007). Based on J_{max}, the default absorption values proposed were as follows:

- Material with J_{max} ≤0.1 μg/cm²/h should be assigned a skin absorption default value of less than 10%.
- If the J_{max} value is >0.1 μg/cm²/h but ≤10 μg/cm²/h, the default skin absorption assigned did not exceed 40%.
- If a material had a J_{max} of >10 μg/cm²/h, the default skin absorption assigned was no more than 80%.

The three default skin absorption percentages were proposed to represent low absorbed, medium absorbed, and high absorbed material. These default values were derived from a broad range of 15 cosmetic ingredients and considered several worst-case assumptions such as, (i) cosmetic ingredients are present at saturation levels, (ii) no depletion of the ingredient occurs during the exposure period, (iii) the formulation does not affect the skin barrier, and (iv) by using the maximal flux over the entire exposure time, the lower flux during the lag time is ignored (Kroes et al., 2007). In another study, Guy proved that the skin absorption of chemicals may be classified by their calculated J_{max} (Guy, 2010). Using the same model, the J_{max} of 20 fragrance materials were calculated and 16 of them were taken one step further to calculate their absorption percentage by including the applied dose, area and time. Over-prediction was observed in 14 materials and therefore, this approach could also be considered an extreme estimation of absorption.

Based on the abovementioned studies, it is apparent that the key to determining a substance's default absorption value is to get an accurate J_{max}. Centered on this reasoning, we propose an *in silico* semi-quantitative mechanistic model for assigning the same default skin absorption values as proposed by Kroes et al. (2007), but specifically constructed around the fragrance material (Fig. 1). As we will show, their overall methodology can be applied to derive similar absorption values for RIFM's fragrance materials that lack experimental skin absorption data, provided we tailor the model to specifically fit a defined set of fragrance material physicochemical parameters. Our mechanistic model was validated with a fragrance-focused data set containing 131 materials. All resulted in predicted values fitting the proposed three-tiered SAM based on J_{max} ranges.

2. Methodology development and data sets

2.1. Defining the chemical space of fragrance materials

Getting insight into the chemical space of fragrance materials and where this space is located in the chemical universe was instructive for us to get the big picture and develop a fragrance-focused SAM. Herein, 2120 fragrance materials with known chemical structure in RIFM database were reviewed. The fragrance chemical space was profiled using three physicochemical properties that significantly influence the overall absorption of a topically applied substance, namely, molecular weight (MW), **log** K_{ow} (octanol/water partition coefficient) and water solubility (S). For perspective, these were compared to more than half a million industry chemicals from the United States Environmental Protection Agency (USEPA) ACTOR database (Judson et al., 2012).

As shown in Fig. 2, the *MW*, **log** K_{ow} and **log** S values of ~500,000 industry chemicals from USEPA ACTOR database are calculated using EPI Suite (USEPA) and plotted to represent the chemical universe (Fig. 2A, blue dots). The same parameters of 2120 fragrance materials are also calculated and plotted in the same chart (Fig. 2A, red dots). Clearly, not only the number of fragrance material is significantly small, but the fragrance space is limited. Further analysis indicates that more than 99% of fragrance materials gave a *MW* ranging from 30 to 330 (Fig. 2B), a **log** K_{ow} from –1 to 9 (Fig. 2C), and **log** S from –9 to 1 (Fig. 2D). As such, we consider any materials falling within these ranges as "fragrance-like" materials.

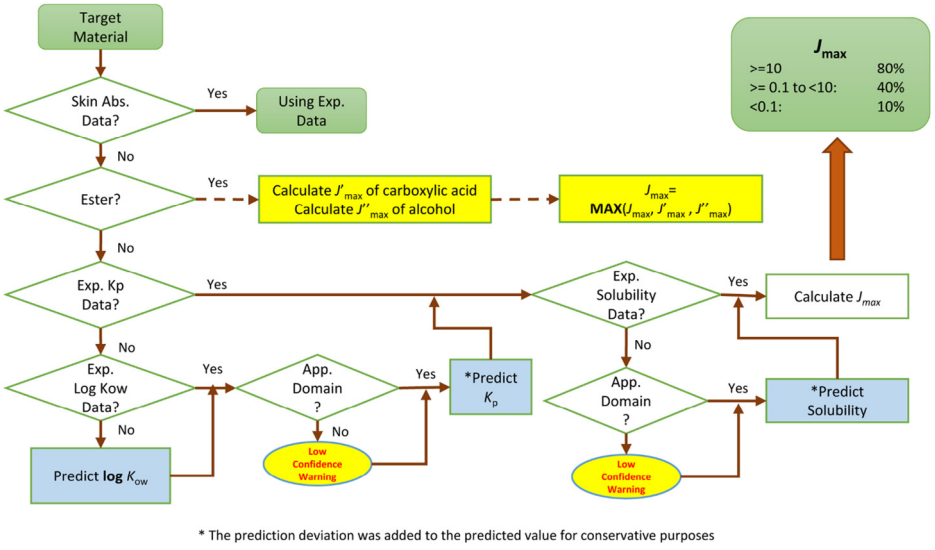

Fig. 1. Workflow for applying the skin absorption model (SAM) in safety assessment. For a target material, first, look for available skin absorption data. If an experimental value is not available, look for experimentally derived K_p and water solubility values to calculate J_{max}. If an experimentally derived K_p is not available, look for an experimentally derived **log** K_{ow}, or use consensus value to estimate the **log** K_{ow}, to determine a predicted K_p using Eq. (4). This predicted K_p may be used with experimentally derived or predicted solubility values to calculate J_{max}. Then the percent skin absorption is estimated based on Eq. (8). If the fragrance material is an ester, one needs to calculate the J_{max} of the parent and breakdown products (i.e., carboxylic acid and alcohol moieties). For conservative purposes accept the value that gives the highest skin absorption.

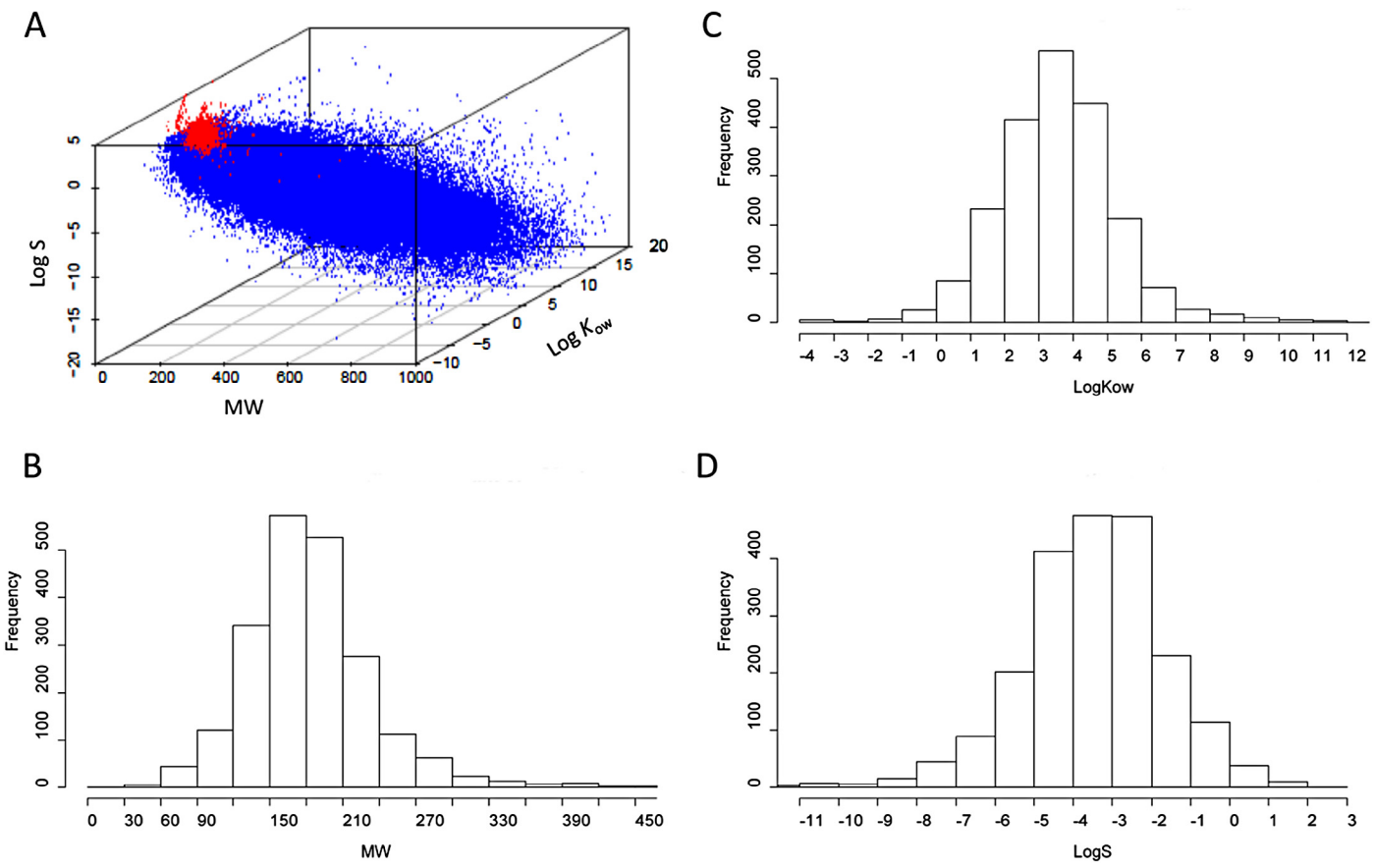

Fig. 2. The fragrance chemical space depicted using *MW*, **log** K_{ow} and **log** *S*. (A) The overlap of 2120 fragrance materials (red dots) from RIFM's database on ~500,000 industry chemicals from USEPA ACTOR database (blue dots). (B) The histogram of *MW* of 2120 fragrance materials. (C) The histogram of **log** K_{ow} of 2120 fragrance materials. (D) The histogram of **log** *S* of 2120 fragrance materials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Datasets for validating and refining SAM

An important step in calculating J_{max} is to get the K_p – the permeability coefficient. Potts and Guy's equation was proposed to be used for calculating the K_p (Potts and Guy, 1992). In order to evaluate the suitability of the Potts and Guy's equation, 105 materials falling within the fragrance chemical space with experimentally determined K_p and **log** K_{ow} values were collected as data set I. Some of that data came from the Flynn data set (Flynn, 1990) that was used to develop the original K_p equation by Potts and Guy (1992). The rest came from EDETOX dataset (Table 1). To validate SAM, 131 materials falling within the fragrance chemical space, with experimentally determined (via *in vitro* or *in vivo* methods) percent skin absorption from using either human or pig skin were collected as data set II (Table 2). Rat data were excluded from this study due to the significant species difference between rat and human (van Ravenzwaay and Leibold, 2004). Of the validation material, 54 were fragrance materials and 77 were "fragrance-like" materials. Forty-five (45) were collected from RIFM's database (Api et al., 2013; Barber et al., 1992; Bickers et al., 2005; Bobin et al., 1997; Bronaugh et al., 1990; Cross et al., 1998; Ford et al., 1999, 2001; Gilpin et al., 2010; Green et al., 2008; Green et al., 2014; Green and Brain, 2001, 2005; Green and Walters, 2006; Hawkins et al., 1994, 1995, 2002; Hotchkiss, 1998; Isola and Api, 2002; Jimbo, 1983; Keith, 2003; Kraeling and Bronaugh, 1997, 2003; Liu and Hotchkiss, 1997; Madsen et al., 2011; Politano et al., 2013; Smith et al., 2000; Tonge, 1995; Watkinson et al., 1992; Yang et al., 1994; Yano et al., 1986), and 86 from the EDETOX database (Williams, 2004). Of the 54 fragrance materials, 52 had human data (46 *in vitro*, six *in vivo*) and two had pig data (*in vitro*). Of the 77 "fragrance-like" materials, 72 had human data (46 *in vitro*, 26 *in vivo*) and five had pig data (two *in vitro*, three *in vivo*). Our validation data set contained 96 materials with experimentally determined **log** K_{ow}, 81 with experimentally determined water solubility (C_{water}^{Sat}), and 27 had an experimentally determined K_p. Twenty-two had all three parameters experimentally derived.

2.3. Calculating J_{max}

As shown in Equation (Eq. (1)) below, J_{max} is calculated from two parameters – the permeability coefficient (K_p) used to characterize the diffusion of chemicals through membranes expressed as cm/h (Hostynek, 2008), and saturated water solubility (C_{water}^{Sat}, in the unit of mg/L or μg/cm^3).

$$J_{max}(\mu g/cm^2/h) = K_p(cm/h) \times C_{water}^{sat}(\mu g/cm^3) \quad (1)$$

2.3.1. Calculate K_p

As shown above, one of the important parameters to calculate J_{max} is K_p. In most cases, the experimental determined K_p is not available. Therefore, a proper QSAR model could be useful to get an estimated K_p. Kroes et al. (2007) proposed to use Potts and Guy's equation (Eq. (2)), which was derived from the Flynn data set of 93 materials with experimentally determined K_p (Flynn, 1990).

$$\mathbf{log}\,K_p(cm/h) = -2.7 + 0.71 \times \mathbf{log}\,K_{ow} - 0.0061 \times MW \quad (2)$$

($n = 93$, $r^2 = 0.67$, SE = 0.794, F = 84.05)

Table 1
Predicted and experimentally determined K_p and K_{ow} of 105 fragrance and "fragrance-like" materials.

Material name	CAS	*MW*	**log** K_{ow}		**log** K_p (cm/h)			Source
			Exp.	Est.	Exp.	Guy's Eq.	RIFM's Eq.	
17α-Hydroxyprogesterone	68-96-2	330.47	3.17	3.15	–3.22	–2.47	–3.44	Flynn set
2-(2-Butoxyethoxy)ethanol	112-34-5	162.23	0.56	0.65	–4.45	–3.29	–3.44	EDETOX
2-(2-Ethoxyethoxy)ethanol	111-90-0	134.18	–0.54	–0.32	–3.88	–3.90	–3.94	EDETOX
2,3-Butanediol	513-85-9	90.12	–0.92	–0.41	–4.40	–3.90	–3.71	Flynn set
2,4,6-Trichlorophenol	25167-82-2	197.45	3.69	3.57	–1.23	–1.28	–1.48	Flynn set
2,4-Dichlorophenol	120-83-2	163.00	3.06	2.93	–1.22	–1.52	–1.55	Flynn set
2-Butanone	78-93-3	72.11	0.29	0.52	–2.35	–2.93	–2.58	Flynn set
2-Butoxyethanol	111-76-2	118.18	0.83	0.78	–3.67	–2.83	–2.71	EDETOX
2-Chlorophenol	25167-80-0	128.56	2.15	2.25	–1.48	–1.96	–1.83	Flynn set
2-Cresol	95-48-7	108.14	1.95	2.05	–1.80	–1.98	–1.75	Flynn set
2-Ethoxy ethanol	110-80-5	90.12	–0.32	–0.23	–3.60	–3.48	–3.26	Flynn set
2-Isopropoxyethanol	109-59-1	104.15	0.05	0.17	–3.36	–3.30	–3.14	EDETOX
2-Methoxyethanol	109-86-4	76.10	–0.77	–0.64	–2.54	–3.71	–3.43	EDETOX
2-Naphthol	135-19-3	144.17	2.70	2.71	–1.55	–1.66	–1.60	Flynn set
2-Phenoxyethanol	122-99-6	138.17	1.16	1.18	–2.87	–2.72	–2.70	EDETOX
2-Phenylphenol	90-43-7	170.21	3.09	3.21	–1.80	–1.54	–1.61	EDETOX
3,4-Xylenol	95-65-8	122.17	2.23	2.52	–1.44	–1.86	–1.70	Flynn set
3-Cresol	108-39-4	108.14	1.96	2.06	–1.82	–1.97	–1.74	Flynn set
3-Nitrophenol	554-84-7	139.11	2.00	1.68	–2.25	–2.13	–2.07	Flynn set
3-Phenyl-1-propanol	1335-12-2	136.20	1.88	1.96	–1.28	–2.20	–2.13	EDETOX
4-Bromophenol	106-41-2	173.01	2.59	2.41	–1.44	–1.92	–2.03	Flynn set
4-Chlorocresol	1570-64-5	142.59	2.78	2.72	–1.26	–1.60	–1.52	Flynn set
4-Chlorophenol	106-48-9	128.56	2.39	2.27	–1.44	–1.79	–1.65	Flynn set
4-Cresol	1319-77-3	108.14	1.94	2.06	–1.75	–1.98	–1.75	Flynn set
4-Ethyl phenol	123-07-9	122.17	2.58	2.56	–1.46	–1.61	–1.43	Flynn set
4-Nitrophenol	100-02-7	139.11	1.91	1.67	–2.25	–2.19	–2.14	Flynn set
5-Fluorouracil	51-21-8	130.08	–0.89	–0.82	–4.78	–4.13	–4.16	EDETOX
Acetylsalicylic acid	50-78-2	180.16	1.19	1.26	–2.14	–2.95	–3.17	EDETOX
Amobarbital	57-43-2	226.28	2.07	1.92	–2.64	–2.61	–3.05	Flynn set
Atropine	51-55-8	289.38	1.83	1.85	–4.12	–3.17	–3.97	Flynn set
Barbital	57-44-3	184.20	0.65	0.67	–3.95	–3.36	–3.63	Flynn set
Benzene	71-43-2	78.11	2.13	1.97	–0.95	–1.66	–1.25	EDETOX
Benzoic acid	65-85-0	122.12	1.87	1.69	–1.60	–2.12	–1.97	EDETOX
Benzyl alcohol	100-51-6	108.14	1.10	1.14	–2.22	–2.58	–2.39	Flynn set
Benzyl nicotinate	94-44-0	213.24	2.40	2.34	–1.80	–2.30	–2.64	EDETOX
Boric acid	10043-35-3	61.83	0.17	–0.74	–3.30	–2.96	–2.55	EDETOX
Butobarbital	77-28-1	212.25	1.73	1.65	–3.71	–2.77	–3.14	Flynn set
Butyl 4-hydroxybenzoate	94-26-8	194.23	3.57	3.15	–2.15	–1.35	–1.53	EDETOX
Butyl nicotinate	6938-06-3	179.22	2.27	2.08	–1.78	–2.18	–2.34	EDETOX
Butyric acid	107-92-6	88.11	0.79	0.88	–3.00	–2.68	–2.39	Flynn set
Caffeine	58-08-2	194.19	–0.07	–0.26	–3.59	–3.93	–4.29	EDETOX
Chlorocresol	59-50-7	142.59	3.10	2.78	–1.26	–1.37	–1.28	EDETOX
Chloroxylenol	88-04-0	156.61	3.27	3.22	–1.28	–1.33	–1.32	Flynn set
Chlorpheniramine	113-92-8	274.80	3.38	3.64	–2.66	–1.98	–2.63	Flynn set
cis-1,3-Dichloropropene	10061-01-5	110.97	2.03	1.91	–0.10	–1.94	–1.72	EDETOX
Codeine	76-57-3	299.37	1.19	1.41	–4.31	–3.68	–4.58	Flynn set
Cortexone	64-85-7	330.47	2.88	3.15	–3.35	–2.67	–3.66	Flynn set
Coumarin	91-64-5	146.15	1.39	1.76	–2.04	–2.60	–2.62	EDETOX
Diclofenac	15307-86-5	296.15	4.51	4.39	–3.00	–1.30	–2.02	EDETOX
Dimethylethylamine	598-56-1	73.14	0.70	0.62	–2.40	–2.65	–2.28	EDETOX
Dimethylformamide	68-12-2	73.10	–1.01	–0.60	–2.02	–3.86	–3.58	EDETOX
DMP	131-11-3	194.19	1.60	1.75	–4.48	–2.75	–3.03	EDETOX
Ephedrine	299-42-3	165.24	1.13	1.10	–2.22	–2.91	–3.04	Flynn set
Estradiol	50-28-2	272.39	4.01	3.82	–2.40	–1.51	–2.12	Flynn set
Estriol	50-27-1	288.39	2.45	2.71	–4.40	–2.72	–3.49	Flynn set
Estrone	53-16-7	270.37	3.13	3.85	–2.44	–2.13	–2.76	Flynn set
Ethanol	64-17-5	46.07	–0.31	–0.17	–3.10	–3.20	–2.73	Flynn set
Ethyl benzene	100-41-4	106.17	3.15	2.97	0.08	–1.11	–0.81	Flynn set
Ethyl ether	60-29-7	74.12	0.89	0.90	–1.80	–2.52	–2.15	Flynn set
Ethyl nicotinate	614-18-6	151.17	1.32	1.10	–2.18	–2.68	–2.73	EDETOX
Heptanoic acid	111-14-8	130.19	2.42	2.36	–1.70	–1.78	–1.65	Flynn set
Hexanoic acid	142-62-1	116.16	1.92	1.87	–1.85	–2.05	–1.86	Flynn set
Ibuprofen	15687-27-1	206.29	3.97	3.69	–1.44	–1.14	–1.37	EDETOX
Isoquinoline	119-65-3	129.16	2.08	1.91	–1.78	–2.01	–1.89	Flynn set
m-Cresol	108-39-4	108.14	1.96	2.06	–1.82	–1.97	–1.74	EDETOX
MDA	101-77-9	198.27	1.59	2.21	–2.64	–2.78	–3.08	EDETOX
Meperidine	57-42-1	247.34	2.72	2.61	–2.43	–2.28	–2.80	Flynn set
Methanol	67-56-1	32.04	–0.77	–0.64	–3.30	–3.44	–2.91	Flynn set
Methyl nicotinate	93-60-7	137.14	0.83	0.66	–2.47	–2.95	–2.94	EDETOX
Methyl-4-hydroxy benzoate	99-76-3	152.15	1.96	1.72	–2.04	–2.24	–2.26	Flynn set
Morphine	57-27-2	285.35	0.89	1.01	–5.03	–3.81	–4.64	Flynn set
N,N-Diethyl-m-toluamide	134-62-3	191.28	2.18	2.45	–2.89	–2.32	–2.55	EDETOX
Naproxen	22204-53-1	230.27	3.18	3.07	–2.54	–1.85	–2.25	Flynn set

(*continued on next page*)

Table 1 (*continued*)

Material name	CAS	*MW*	**log** K_{ow}		**log** K_p (cm/h)			Source
			Exp.	Est.	Exp.	Guy's Eq.	RIFM's Eq.	
n-Butanol	71-36-3	74.12	0.88	0.86	–2.60	–2.53	–2.16	Flynn set
n-Decanol	112-30-1	158.29	4.57	3.90	–1.10	–0.42	–0.35	Flynn set
n-Heptanol	111-70-6	116.21	2.62	2.37	–1.50	–1.55	–1.33	Flynn set
n-Hexanol	111-27-3	102.18	2.03	1.87	–1.89	–1.88	–1.61	Flynn set
N-Hexyl nicotinate	23597-82-2	207.27	3.51	3.06	–1.75	–1.47	–1.73	EDETOX
Nicotine	54-11-5	162.24	1.17	1.14	–2.48	–2.86	–2.98	Flynn set
Nicotinic acid	59-67-6	123.11	0.36	0.22	–4.62	–3.20	–3.13	EDETOX
Nitroglycerine	100292-13-5	227.09	1.62	1.61	–1.96	–2.94	–3.40	Flynn set
n-Nonanol	143-08-8	144.26	3.77	3.38	–1.22	–0.90	–0.79	Flynn set
n-Octanol	111-87-5	130.23	3.00	2.88	–1.28	–1.36	–1.21	Flynn set
n-Pentanol	71-41-0	88.15	1.51	1.38	–2.22	–2.17	–1.84	Flynn set
n-Propanol	71-23-8	60.10	0.25	0.35	–2.85	–2.89	–2.47	Flynn set
o-Cresol	95-48-7	108.14	1.95	2.05	–1.80	–1.98	–1.75	EDETOX
Octanoic acid	124-07-2	144.22	3.05	2.86	–1.60	–1.41	–1.34	Flynn set
Parathion	56-38-2	291.26	3.83	3.43	–3.72	–1.76	–2.48	EDETOX
p-Cresol	106-44-5	108.14	1.94	2.06	–1.76	–1.98	–1.75	EDETOX
Pentanoic acid	109-52-4	102.13	1.39	1.38	–2.70	–2.34	–2.10	Flynn set
Phenobarbital	11097-06-6	232.24	1.47	1.35	–3.34	–3.07	–3.57	Flynn set
Phenol	108-95-2	94.11	1.46	1.55	–2.09	–2.24	–1.95	Flynn set
Pregnenolone	145-13-1	316.49	4.22	3.80	–2.82	–1.63	–2.48	Flynn set
Progesterone	57-83-0	314.47	3.87	3.87	–2.82	–1.87	–2.72	Flynn set
Propoxur	114-26-1	209.25	1.52	2.04	–2.59	–2.90	–3.26	EDETOX
Propranolol	525-66-6	259.35	3.48	2.80	–2.77	–1.81	–2.37	EDETOX
Resorcinol	108-46-3	110.11	0.80	1.13	–3.62	–2.80	–2.64	Flynn set
Salicylic acid	69-72-7	138.12	2.26	1.91	–1.86	–1.94	–1.86	Flynn set
Scopolamine	51-34-3	303.36	0.98	1.01	–4.30	–3.85	–4.78	Flynn set
Styrene	100-42-5	104.15	2.95	2.72	–0.19	–1.24	–0.94	Flynn set
Testosterone	58-22-0	288.43	3.32	3.29	–2.66	–2.10	–2.83	Flynn set
Thymol	89-83-8	150.22	3.30	3.32	–1.28	–1.27	–1.22	Flynn set
Toluene	108-88-3	92.14	2.73	2.48	0.00	–1.32	–0.97	Flynn set
Trichloromethane	67-66-3	119.38	1.97	1.84	–1.80	–2.03	–1.86	EDETOX
Trimethylamine	75-50-3	59.11	0.16	0.17	–3.72	–2.95	–2.53	EDETOX

exp. = experimentally determined, est. = estimated.

Before applying Potts and Guy's equation (Potts and Guy, 1992), we refined the parameters by re-running the multiple linear regression based on the data set I. As mentioned above, data set I contains 105 materials falling within the fragrance chemical space with experimentally determined **log** K_{ow} and K_p. Specifically, the independent variables are **log** K_{ow} and *MW*, the dependent variable is the **log** K_p. Least square was performed to fit the parameters of the linear equation. The updated Eq. (3) with newly fitted parameters was used to calculate **log** K_p for the materials falling in the fragrance chemical space.

$$\mathbf{log}K_p(cm/h) = -1.95 + 0.759 \times \mathbf{log}K_{ow} - 0.0118 \times MW \quad (3)$$

($n = 105$, $r^2 = 0.703$, SE = 0.594, F = 120.56)

Note that the standard error of estimation (SE) of the above equation (Eq. (3)) is 0.594. For conservative purposes, this number is added to the predicted **log** K_p before using it to calculate the J_{max}. Therefore, the following Eq. (4) is used to estimate the conservative K_p:

$$\mathbf{log}K_p(cm/h) = -1.356 + 0.759 \times \mathbf{log}K_{ow} - 0.0118 \times MW \quad (4)$$

It is worth noting that the viable skin layers beneath the stratum corneum could contribute to the penetration rate for very lipophilic chemicals. Cleek and Bunge (1993) took this into consideration and proposed the algebraic Eq. (5) to modify for K_p. Taking this into consideration, Eq. (1) is more correctly stated as Eq. (6).

$$K_p^{corr}(cm/h) = \frac{K_p}{1 + \frac{K_p \times \sqrt{MW}}{2.6}} \quad (5)$$

$$J_{max}(\mu g/cm^2/h) = K_p^{corr}(cm/h) \times C_{water}^{sat}(\mu g/cm^3) \quad (6)$$

2.3.2. Calculate **log** K_{ow}

As shown in Eq. (4), the K_p is calculated based on **log** K_{ow} and *MW*. If the experimental **log** K_{ow} is unknown, different QSAR prediction models could be used to calculate the **log** K_{ow}. There are two key factors for a QSAR model, molecular descriptors and training algorithms. Molecular descriptors are a series of parameters calculated based on molecular structure, which can be understood by a mathematics algorithm. The training algorithm is the core of building a QSAR model. Different molecular descriptors and algorithms could build QSAR models with different preferences and performance. It has been suggested that using a consensus model based on the average prediction of different models could yield more accurate results than individual models (Mannhold et al., 2009; Tetko et al., 2009). Therefore, in this work, seven different models with different algorithms and descriptors are used to compose a consensus model (Table 3). The seven models were selected based on molecular descriptor, modeling algorithm, training set, and accessibility. The idea is to cover different models with diverse descriptors, algorithms and training sets to obtain a more representative outcome. These seven models were also validated in their original papers with a high accuracy. The average value of the seven predictions is used as the final output of the predicted **log** K_{ow}.

2.3.3. Calculate water solubility (C_{water}^{Sat})

As shown in Eq. (1), another parameter for calculating J_{max} is the saturated water solubility (C_{water}^{sat}) in the units of mg/L, which equals μg/cm³. Like the **log** K_{ow}, when experimental data is lacking, the consensus prediction from four different QSAR models is used to estimate the water solubility (S) in the units of mol/L (Table 4). However, one should note that the water solubility models are not as accurate as those of **log** K_{ow}. The root-mean-square

Table 2
Estimated and experimentally determined skin absorption values for 131 fragrance and fragrance like materials.

ID	Material name	CAS	*MW*	**log** K_{ow}	C_{water}^{Sat} (μg/cm^3)	**log** K_p	K_p (cm/h)	K_p^{corr} (cm/h)	J_{max} (μg/cm^2/h)	Absorption (%)		
										Est.	Exp.	Source
1	Musk ketone	81-14-1	294.31	4.30[a]	1.9[a]	–1.559	2.76E-02	2.33E-02	0.04	10	0.5	RIFM Db
2	Acetyl cedrene	32388-55-9	246.4	4.20	45.2	–1.071	8.50E-02	5.62E-02	2.54	40	13.52	RIFM Db
3	1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone	54464-57-2	234.38	4.31	60	–0.846	1.43E-01	7.75E-02	4.65	40	16.51	RIFM Db
4	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	21145-77-7	258.41	5.70[a]	1.3[a]	–0.073	8.45E-01	1.36E-01	0.17	40	0.88	EDETOX
5	Farnesol	4602-84-0	222.37	4.75	27.6	–0.366	4.31E-01	1.24E-01	3.42	40	39.8	RIFM Db
6	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran	1222-05-5	258.41	5.90[a]	1.8[a]	0.079	1.20E+00	1.43E-01	0.25	40	5.16	RIFM Db
7	α-Hexylcinnamaldehyde	101-86-0	216.33	4.68	25.3	–0.348	4.49E-01	1.27E-01	3.21	40	9.54	RIFM Db
8	p-t-Butyl-α-methylhydrocinnamic aldehyde	80-54-6	204.31	4.07	42.7	–0.671	2.13E-01	9.82E-02	4.19	40	30	RIFM Db
9	Benzyl benzoate	120-51-4	212.25	3.97[a]	167.1	–0.841	1.44E-01	7.97E-02	13.32	80	71.2	RIFM Db
	Benzoic acid		122.12	1.87[a]	3400[a]	–1.602[a]	2.50E-02	2.26E-02	76.84			
	Benzyl alcohol		108.14	1.10[a]	42900[a]	–2.220[a]	6.03E-03	5.88E-03	252.41			
10	Benzyl salicylate	118-58-1	228.25	3.74	357.8	–1.209	6.18E-02	4.54E-02	16.26	80	15	RIFM Db
	2-Hydroxybenzoic acid		138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10			
	Benzyl alcohol		108.14	1.10[a]	42900[a]	–2.220[a]	6.03E-03	5.88E-03	252.41			
11	Amyl salicylate	2050-08-0	208.26	4.00	421.1	–0.774	1.68E-01	8.70E-02	36.62	80	10.3	RIFM Db
	2-Hydroxybenzoic acid		138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10			
	Amyl alcohol		88.15	1.51[a]	22000[a]	–2.220[a]	6.03E-03	5.90E-03	129.74			
12	d-Limonene	5989-27-5	136.24	4.38[a]	13.8[a]	0.361	2.30E+00	2.03E-01	2.80	40	5	RIFM Db
13	Butyl salicylate	2052-14-4	194.23	4.63[a]	1326.9	–0.134	7.35E-01	1.49E-01	197.43	80	17.1	RIFM Db
	2-Hydroxybenzoic acid		138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10			
	Butyl alcohol		74.12	0.88[a]	63200[a]	–2.600[a]	2.51E-03	2.49E-03	157.44			
14	α-Methyl-1,3-benzodioxole-5-propionaldehyde	1205-17-0	192.22	2.14	1390	–1.996	1.01E-02	9.57E-03	13.30	80	50.1	RIFM Db
15	Methyl dihydrojasmonate	24851-98-7	226.32	2.80	280[a]	–1.899	1.26E-02	1.18E-02	3.29	80	45.9	RIFM Db
	(3-oxo-2-pentylcyclopentyl)acetic acid		212.29	2.59	5547	–1.896	1.27E-02	1.19E-02	65.76			
	Methanol		32.04	–0.77[a]	1000000[a]	–3.300[a]	5.01E-04	5.01E-04	500.64			
16	Safrole	94-59-7	162.19	2.80	592.2	–1.142	7.21E-02	5.33E-02	31.56	80	38.4	EDETOX
17	Isoeugenol	97-54-1	164.21	3.04[a]	1164	–0.986	1.03E-01	6.84E-02	79.63	80	38.4	RIFM Db
18	2-Methoxy-4-propylphenol	2785-87-7	166.22	2.94	1531	–1.085	8.21E-02	5.84E-02	89.36	80	22.6	RIFM Db
19	2-Methoxy-4-vinylphenol	7786-61-0	150.18	2.20	2585.2	–1.455	3.51E-02	3.01E-02	77.85	80	38.4	RIFM Db
20	dl-Citronellol	106-22-9	156.27	3.91[a]	575	–0.232	5.86E-01	1.53E-01	88.26	80	4.7	RIFM Db
21	Eugenyl methyl ether	93-15-2	178.23	2.94	500[a]	–1.231	5.87E-02	4.51E-02	22.56	80	49.7	RIFM Db
22	Dihydromyrcenol	18479-58-8	156.27	3.11	1177.2	–0.839	1.45E-01	8.54E-02	100.49	80	5.67	RIFM Db
23	Coumarin	91-64-5	146.15	1.39[a]	1900[a]	–2.040[a]	9.12E-03	8.75E-03	16.62	80	59.7	RIFM Db
24	Dihydro-α-terpineol	498-81-7	156.27	2.97	1656.3	–0.943	1.14E-01	7.37E-02	122.06	80	3.5	RIFM Db
25	Benzyl acetate	140-11-4	150.18	1.96[a]	3100[a]	–1.640	2.29E-02	2.07E-02	64.03	80	78.7	RIFM Db
	Acetic acid		60.05	–0.17[a]	1000000[a]	–2.194	6.40E-03	6.28E-03	6283.04			
	Benzyl alcohol		108.14	1.10[a]	42900[a]	–2.220[a]	6.03E-03	5.88E-03	252.41			
26	Eugenol	97-53-0	164.21	2.27[a]	2460[a]	–1.571	2.69E-02	2.37E-02	58.37	80	22.6	RIFM Db
27	Cinnamic acid	621-82-9	148.16	2.13[a]	570[a]	–1.488	3.25E-02	2.82E-02	16.09	80	60.8	RIFM Db
28	Diethyl malonate	105-53-3	160.17	0.96[a]	23200[a]	–2.517	3.04E-03	2.99E-03	69.46	80	54.3	EDETOX
	Malonic acid		104.06	–0.81[a]	763000[a]	–3.199	6.33E-04	6.31E-04	481.67			
	Ethyl alcohol		46.07	–0.31[a]	1000000[a]	–3.100[a]	7.94E-04	7.93E-04	792.68			
	Ethyl hydrogen malonate		132.12	0.14	280141.3	–2.807	1.56E-03	1.55E-03	434.21			
29	Benzoic acid	65-85-0	122.12	1.87[a]	3400[a]	–1.602[a]	2.50E-02	2.26E-02	76.85	80	60.6	EDETOX
30	Methyl salicylate	119-36-8	152.15	2.55[a]	700[a]	–1.216	6.08E-02	4.72E-02	33.04	80	30.7	RIFM Db
	2-Hydroxybenzoic acid		138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10			
	Methanol		32.04	–0.77[a]	1000000[a]	–3.300[a]	5.01E-04	5.01E-04	500.64			
31	Geraniol	106-24-1	154.25	3.47[a]	531[a]	–0.542	2.87E-01	1.21E-01	64.26	80	7.3	RIFM Db
32	Linalool	78-70-6	154.25	2.97[a]	1590[a]	–0.922	1.20E-01	7.62E-02	121.08	80	14.4	RIFM Db
33	2-Hydroxybenzoic acid	69-72-7	138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10	80	22.78	EDETOX
34	Cinnamyl alcohol	104-54-1	134.18	1.95[a]	7112.7	–1.459	3.47E-02	3.01E-02	213.93	80	65.9	RIFM Db
35	2-Phenoxyethanol	122-99-6	138.17	1.16[a]	26700[a]	–2.870[a]	1.35E-03	1.34E-03	35.80	80	59.3	EDETOX
36	Phenethyl alcohol	60-12-8	122.17	1.36[a]	22200[a]	–1.765	1.72E-02	1.60E-02	355.14	80	7.6	RIFM Db
37	Benzyl alcohol	100-51-6	108.14	1.10[a]	42900[a]	–2.220[a]	6.03E-03	5.88E-03	252.41	80	14.97	EDETOX
38	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	31906-04-4	210.32	2.56	6100[a]	–1.896	1.27E-02	1.19E-02	72.41	80	36.4	RIFM Db
39	Phenol	108-95-2	94.11	1.46[a]	82800[a]	–2.090[a]	8.13E-03	7.89E-03	653.21	80	47.1	EDETOX
40	Ethyl alcohol	64-17-5	46.07	–0.31[a]	1000000[a]	–3.100[a]	7.94E-04	7.93E-04	792.68	80	21.17	EDETOX
41	Geranyl nitrile	5146-66-7	149.24	3.24	373.2	–0.654	2.22E-01	1.09E-01	40.52	80	5.05	RIFM Db
42	Trichloromethyl phenyl carbinyl acetate	90-17-5	267.54	3.43	393.7	–1.907	1.24E-02	1.15E-02	4.52	40	5	RIFM Db
	Acetic acid		60.05	–0.17[a]	1000000[a]	–2.194	6.40E-03	6.28E-03	6283.04			
	2,2,2-trichloro-1-phenylethanol		225.5	2.86	2123.4	–1.849	1.42E-02	1.31E-02	27.81			

(*continued on next page*)

Table 2 (*continued*)

ID	Material name	CAS	*MW*	**log** K_{ow}	C_{water}^{Sat} (μg/cm^3)	**log** K_p	K_p (cm/h)	K_p^{corr} (cm/h)	J_{max} (μg/cm^2/h)	Absorption (%)		
										Est.	Exp.	Source
43	Methyl atrarate	4707-47-5	196.2	2.56	11039.9	–1.729	1.87E-02	1.70E-02	187.25	80	20	RIFM Db
	2,4-dihydroxy-3,6-dimethylbenzoic acid		182.18	2.19	26284.3	–1.843	1.43E-02	1.33E-02	350.88			
	Methanol		32.04	–0.77[a]	1000000[a]	–3.300[a]	5.01E-04	5.01E-04	500.64			
44	Lactic acid	50-21-5	90.08	–0.72[a]	1000000[a]	–2.965	1.08E-03	1.08E-03	1078.61	80	10.12	RIFM Db
45	2-Methyl-2-propanol	75-65-0	74.12	0.35[a]	1000000[a]	–1.965	1.08E-02	1.05E-02	10464.50	80	2	RIFM Db
46	Triethanolamine	102-71-6	149.19	–1.00[a]	1000000[a]	–3.875	1.33E-04	1.33E-04	133.13	80	6.9	RIFM Db
47	Diethyl maleate	141-05-9	172.18	1.30	14000[a]	–2.398	4.00E-03	3.92E-03	54.91	80	54	RIFM Db
	Maleic acid		116.07	0.46[a]	7000[a]	–2.376	4.20E-03	4.13E-03	28.91			
	Ethyl alcohol		46.07	–0.31[a]	1000000[a]	–3.100[a]	7.94E-04	7.93E-04	792.68			
	4-ethoxy-4-oxobut-2-enoic acid		144.13	0.66	265639.8	–2.556	2.78E-03	2.75E-03	729.67			
48	2-Ethyl-1-hexanol	104-76-7	130.23	2.69	880[a]	–0.853	1.40E-01	8.69E-02	76.46	80	5.2	RIFM Db
49	1-Decanol	112-30-1	158.29	4.57[a]	37[a]	–1.100[a]	7.94E-02	5.74E-02	2.12	40	0.02	RIFM Db
50	Octanoic acid	124-07-2	144.22	3.05[a]	789[a]	–1.600[a]	2.51E-02	2.25E-02	17.76	80	1.77	RIFM Db
51	Lauric acid	143-07-7	200.32	4.60[a]	4.8[a]	–0.228	5.91E-01	1.40E-01	0.67	40	0.164	RIFM Db
52	Methyl 2-nonynoate	111-80-8	168.24	3.57	151.2	–0.628	2.35E-01	1.08E-01	16.37	80	5	RIFM Db
53	Estragole	140-67-0	148.21	3.08	178[a]	–0.764	1.72E-01	9.53E-02	16.96	80	17	RIFM Db
54	Diethyl phthalate	84-66-2	222.24	2.42[a]	1080[a]	–2.142	7.22E-03	6.93E-03	7.48	40	4.7	RIFM Db
	phthalic acid		166.13	0.73[a]	6970[a]	–2.762	1.73E-03	1.71E-03	11.95			
	Ethyl alcohol		46.07	–0.31[a]	1000000[a]	–3.100[a]	7.94E-04	7.93E-04	792.68			
	2-(ethoxycarbonyl)benzoic acid		194.19	1.80	9794.3	–2.282	5.22E-03	5.08E-03	49.78			
55	1,6 Hexanediol diglycidyl ether	16096-31-4	230.31	1.08	37892.4	–3.251	5.61E-04	5.59E-04	21.19	80	37.8	EDETOX
56	17a-Hydroxyprogesterone	68-96-2	330.47	3.17[a]	429.3	–3.220[a]	6.03E-04	6.00E-04	0.26	40	14.76	EDETOX
57	1-Methoxypropan-2-ol	107-98-2	90.12	–0.21	1000000[a]	–2.576	2.66E-03	2.63E-03	2630.55	80	2.29	EDETOX
58	2,4-Dichlorophenoxyacetic acid	94-75-7	221.04	2.81[a]	677[a]	–1.831	1.47E-02	1.36E-02	9.20	40	1.2	EDETOX
59	2-Butoxyethanol	111-76-2	118.18	0.83[a]	1000000[a]	–3.670[a]	2.14E-04	2.14E-04	213.61	80	27.39	EDETOX
60	2-Ethoxyethanol	110-80-5	90.12	–0.32[a]	1000000[a]	–3.600[a]	2.51E-04	2.51E-04	250.96	80	17.8	EDETOX
61	2-Isopropoxyethanol	109-59-1	104.15	0.05[a]	1000000[a]	–3.357[a]	4.40E-04	4.39E-04	438.78	80	1.55	EDETOX
62	2-Methoxyethyl acetate	110-49-6	118.13	0.02	1000000[a]	–2.734	1.85E-03	1.83E-03	1831.24	80	5.37	EDETOX
	Acetic acid		60.05	–0.17[a]	1000000[a]	–2.194	6.40E-03	6.28E-03	6283.04			
	Ethylene glycol methyl ether		76.1	–0.77[a]	1000000[a]	–2.838	1.45E-03	1.44E-03	1443.71			
63	2-Naphthylamine	91-59-8	143.19	2.28[a]	1142.7	–1.315	4.84E-02	3.96E-02	45.23	80	54.1	EDETOX
64	2-Nitro-4-Phenylenediamine	5307-14-2	153.14	0.53[a]	25047.2	–2.761	1.73E-03	1.72E-03	43.09	80	21.7	EDETOX
65	2-phenylphenol	90-43-7	170.21	3.09[a]	700[a]	–1.800[a]	1.58E-02	1.47E-02	10.28	80	26.67	EDETOX
66	4-Acetamidophenol	103-90-2	151.17	0.46[a]	14000[a]	–2.791	1.62E-03	1.61E-03	22.50	80	3.7	EDETOX
67	4-Amino-2-nitrophenol	119-34-6	154.13	0.96[a]	17855.3	–2.446	3.58E-03	3.52E-03	62.85	80	45.1	EDETOX
68	4-Aminobenzoic acid	150-13-0	137.14	0.83[a]	6110[a]	–2.344	4.53E-03	4.44E-03	27.10	80	28.37	EDETOX
69	4-Aminophenol	123-30-8	109.13	0.04[a]	16000[a]	–2.613	2.44E-03	2.41E-03	38.59	80	8.1	EDETOX
70	4-Cyanophenol	767-00-0	119.12	1.60[a]	17543.2	–1.547	2.84E-02	2.53E-02	444.67	80	46	EDETOX
71	4-Dimethylaminobenzene	60-11-7	225.3	4.58[a]	36.9	–0.538	2.90E-01	1.08E-01	4.00	40	21.57	EDETOX
72	4-Heptyloxyphenol	13037-86-0	208.3	4.39	118.9	–0.483	3.29E-01	1.16E-01	13.85	80	36	EDETOX
73	4-Iodophenol	540-38-5	220.01	2.91[a]	4271.7	–1.743	1.81E-02	1.64E-02	69.92	80	28	EDETOX
74	4-Nitroaniline	100-01-6	138.13	1.39[a]	12857.9	–1.931	1.17E-02	1.11E-02	143.16	80	48	EDETOX
75	4-Nitrophenol	100-02-7	139.11	1.91[a]	11600[a]	–1.548	2.83E-02	2.51E-02	291.17	80	41	EDETOX
76	4-Pentyloxyphenol	18979-53-8	180.25	3.50[a]	693.6	–0.826	1.49E-01	8.42E-02	58.44	80	29	EDETOX
77	Acetylcysteine	616-91-1	163.19	–0.46	888507.8	–3.628	2.35E-04	2.35E-04	208.90	80	40.5	EDETOX
78	Acetylsalicylic acid	50-78-2	180.16	1.19[a]	4600[a]	–2.140[a]	7.24E-03	6.98E-03	32.12	80	31.2	EDETOX
	Acetic acid		60.05	–0.17[a]	1000000[a]	–2.194	6.40E-03	6.28E-03	6283.04			
	2-Hydroxybenzoic acid		138.12	2.26[a]	2240[a]	–1.860[a]	1.38E-02	1.30E-02	29.10			
79	Androstenedione	63-05-8	286.42	2.75[a]	322.8	–2.649	2.25E-03	2.21E-03	0.71	40	13.47	EDETOX
80	Aniline	62-53-3	93.13	0.90[a]	36000[a]	–1.772	1.69E-02	1.59E-02	572.84	80	37.6	EDETOX
81	Atrazine	1912-24-9	215.69	2.61[a]	34.7[a]	–1.920	1.20E-02	1.13E-02	0.39	40	3.5	EDETOX
82	Azodrin	6923-22-4	223.17	–0.20[a]	1000000[a]	–4.141	7.22E-05	7.22E-05	72.21	80	14.7	EDETOX
83	Benzocaine	94-09-7	165.19	1.86[a]	1310[a]	–1.894	1.28E-02	1.20E-02	15.75	80	48	EDETOX
	4-Aminobenzoic acid		137.14	0.83[a]	6110[a]	–2.344	4.53E-03	4.44E-03	27.10			
	Ethyl alcohol		46.07	–0.31[a]	1000000[a]	–3.100[a]	7.94E-04	7.93E-04	792.68			
84	Beta-estradiol	50-28-2	272.39	4.01[a]	308.7	–2.400[a]	3.98E-03	3.88E-03	1.20	40	38	EDETOX
85	Boric Acid	10043-35-3	61.83	0.17[a]	50000[a]	–3.301[a]	5.00E-04	4.99E-04	24.96	80	1.75	EDETOX
86	Butachlor	23184-66-9	311.86	4.50[a]	20[a]	–1.620	2.40E-02	2.06E-02	0.41	40	4.4	EDETOX
87	Caffeine	58-08-2	194.19	–0.07[a]	21600[a]	–3.580[a]	2.63E-04	2.63E-04	5.67	40	32.6	EDETOX
88	Carbaryl	63-25-2	201.23	2.36[a]	110[a]	–1.939	1.15E-02	1.08E-02	1.19	40	73.91	EDETOX
	N-methylcarbamate		75.07	–0.52	1412653	–2.638	2.30E-03	2.28E-03	3224.58			
	1-Naphthol		144.17	2.85[a]	866[a]	–0.894	1.28E-01	8.03E-02	69.54			
89	Catechol	120-80-9	110.11	0.88[a]	461000[a]	–1.987	1.03E-02	9.88E-03	4556.62	80	1.8	EDETOX
90	Chloramphenicol	56-75-7	323.13	1.14[a]	2500[a]	–4.304	4.97E-05	4.97E-05	0.12	40	2.9	EDETOX
91	Cinnamyl anthranilate	87-29-6	253.3	3.73	44	–1.512	3.08E-02	2.59E-02	1.14	40	53.3	EDETOX
	Benzoic acid, 2-amino-		137.14	1.21[a]	3500[a]	–2.056	8.79E-03	8.46E-03	29.60			
	Cinnamyl alcohol		134.18	1.95[a]	7113.9	–1.459	3.47E-02	3.01E-02	213.97			
92	Deoxycorticosterone	64-85-7	330.47	2.88[a]	375.9	–3.350[a]	4.47E-04	4.45E-04	0.17	40	12.55	EDETOX
93	DFP	55-91-4	184.15	1.17[a]	15400[a]	–2.641	2.29E-03	2.26E-03	34.79	80	24.3	EDETOX
94	DHEA	53-43-0	288.43	3.23[a]	344.3	–2.308	4.92E-03	4.77E-03	1.64	40	18.45	EDETOX
95	Diazinon	333-41-5	304.35	3.81[a]	105.1	–2.056	8.80E-03	8.31E-03	0.87	40	14.1	EDETOX

(*continued on next page*)

Table 2 (*continued*)

ID	Material name	CAS	*MW*	**log** K_{ow}	C_{water}^{Sat} (μg/cm^3)	**log** K_p	K_p (cm/h)	K_p^{corr} (cm/h)	J_{max} (μg/cm^2/h)	Absorption (%)		
										Est.	Exp.	Source
96	Diethylene glycol monobutyl ether acetate	124-17-4	204.27	1.25	31000[a]	–2.819	1.52E-03	1.50E-03	46.60	80	41.81	EDETOX
	Acetic acid		60.05	–0.17[a]	1000000[a]	–2.194	6.40E-03	6.28E-03	6283.04			
	Diethylene glycol monobutyl ether		162.23	0.56[a]	1000000[a]	–2.845	1.43E-03	1.42E-03	1418.07			
97	Dimethoate	60-51-5	229.25	0.78[a]	23300[a]	–3.469	3.40E-04	3.39E-04	7.90	40	2.6	EDETOX
98	Dimethylnitrosamine	62-75-9	74.08	–0.57[a]	1000000[a]	–2.663	2.17E-03	2.16E-03	2158.30	80	3.98	EDETOX
99	Dinitrochlorobenzene	97-00-7	202.55	2.17[a]	722.8	–2.099	7.96E-03	7.63E-03	5.51	40	27.5	EDETOX
100	Dipropylene glycol methyl ether	34590-94-8	148.2	0.15	571755.2	–2.994	1.01E-03	1.01E-03	577.55	80	0.32	EDETOX
101	Flutamide	13311-84-7	276.22	3.35[a]	315.3	–2.073	8.46E-03	8.02E-03	2.53	40	16.1	EDETOX
102	Hippuric acid	495-69-2	179.18	0.31[a]	3750[a]	–3.235	5.82E-04	5.80E-04	2.18	40	1.2	EDETOX
103	Lindane	58-89-9	290.83	4.14[a]	33.7	–1.646	2.26E-02	1.97E-02	0.66	40	25.7	EDETOX
104	Malathion	121-75-5	330.35	2.36[a]	143[a]	–3.463	3.44E-04	3.44E-04	0.05	10	4.48	EDETOX
105	MbOCA	101-14-4	267.16	3.91[a]	13.9[a]	–1.541	2.88E-02	2.44E-02	0.34	40	5.9	EDETOX
106	MDA	101-77-9	198.27	1.59[a]	1000[a]	–2.644[a]	2.27E-03	2.24E-03	2.24	40	32.9	EDETOX
107	Methiocarb	2032-65-7	225.31	2.92[a]	27[a]	–1.798	1.59E-02	1.46E-02	0.39	40	15.4	EDETOX
	N-methylcarbamate		75.07	–0.52	1412653	–2.638	2.30E-03	2.28E-03	3224.58			
	4-(methylthio)-3,5-xylenol		168.26	3.03	1468.8	–1.043	9.05E-02	6.23E-02	91.57			
108	Methyl-Parathion	298-00-0	263.21	2.86[a]	37.7[a]	–2.291	5.12E-03	4.96E-03	0.19	40	8.99	EDETOX
109	N,N-Diethyl-m-toluamide	134-62-3	191.28	2.18[a]	1045.2	–2.889[a]	1.29E-03	1.28E-03	1.34	40	27.7	EDETOX
110	Nicotinamide	98-92-0	122.13	–0.37[a]	500000[a]	–3.078	8.36E-04	8.33E-04	416.36	80	28.8	EDETOX
111	Nicotinic acid	59-67-6	123.11	0.36[a]	18000[a]	–4.620[a]	2.40E-05	2.40E-05	0.43	40	3.3	EDETOX
112	Nitrobenzene	98-95-3	123.11	1.85[a]	2090[a]	–1.405	3.94E-02	3.37E-02	70.49	80	41.1	EDETOX
113	N-Phenyl-2-naphthylamine	135-88-6	219.29	4.38[a]	17.1	–0.619	2.40E-01	1.01E-01	1.73	40	0	EDETOX
114	n-Propoxyethanol	2807-30-9	104.15	0.28	276663.7	–2.370	4.27E-03	4.20E-03	1160.97	80	3.3	EDETOX
115	o-cresyl glycidyl ether	2210-79-9	164.21	2.10	2095.7	–1.701	1.99E-02	1.81E-02	37.98	80	10.2	EDETOX
116	o-toluidine	95-53-4	107.16	1.32[a]	16600[a]	–1.619	2.41E-02	2.20E-02	364.55	80	49.8	EDETOX
117	Paraoxon	311-45-5	275.2	1.98[a]	3640[a]	–3.101	7.93E-04	7.89E-04	2.87	40	15.52	EDETOX
118	Pentachlorophenol	87-86-5	266.34	5.12[a]	14[a]	–0.613	2.44E-01	9.64E-02	1.35	40	1.5	EDETOX
119	Phosmet	732-11-6	317.32	2.78[a]	24.4[a]	–2.990	1.02E-03	1.02E-03	0.02	10	2.15	EDETOX
120	Phoxim	14816-18-3	298.3	4.39[a]	4.1[a]	–1.544	2.86E-02	2.40E-02	0.10	10	2.9	EDETOX
121	Pirimicarb	23103-98-2	238.29	1.70[a]	2700[a]	–2.878	1.33E-03	1.32E-03	3.55	40	28.2	EDETOX
	Carbamic acid, dimethyl-		89.09	–0.29	1248465	–2.626	2.37E-03	2.35E-03	2929.94			
	2-(dimethylamino)-5,6-dimethylpyrimidin-4-ol		167.21	1.63	47989.3	–2.091	8.11E-03	7.79E-03	373.93			
122	Progesterone	57-83-0	314.47	3.87[a]	8.8[a]	–2.820[a]	1.51E-03	1.50E-03	0.01	10	0.71	EDETOX
123	Propoxur	114-26-1	209.25	1.52[a]	1860[a]	–2.590[a]	2.57E-03	2.53E-03	4.71	40	19.6	EDETOX
	N-methylcarbamate		75.07	–0.52	1412653	–2.638	2.30E-03	2.28E-03	3224.58			
	2-isopropoxyphenol		152.19	2.09[a]	4704.6	–1.566	2.72E-02	2.41E-02	113.31			
124	Propylene glycol	57-55-6	76.1	–0.92[a]	1000000[a]	–2.952	1.12E-03	1.11E-03	1112.03	80	13.8	EDETOX
125	Testosterone	58-22-0	288.43	3.32[a]	270.1	–2.660[a]	2.19E-03	2.16E-03	0.58	40	34.8	EDETOX
126	Theophylline	58-55-9	180.17	–0.04[a]	7360[a]	–3.512	3.07E-04	3.07E-04	2.26	40	16.9	EDETOX
127	Thiourea	62-56-6	76.12	–1.08[a]	142000[a]	–3.074	8.43E-04	8.41E-04	119.43	80	3.4	EDETOX
128	Trichlorocarbanilide	101-20-2	315.59	4.74	17.5	–1.485	3.28E-02	2.68E-02	0.47	40	0.392	EDETOX
129	Trichloromethane	67-66-3	119.38	1.97[a]	7950[a]	–1.796[a]	1.60E-02	1.50E-02	119.16	80	8.2	EDETOX
130	Triclopyr	55335-06-3	256.47	2.76	440[a]	–2.286	5.18E-03	5.02E-03	2.21	40	1.65	EDETOX
131	Trimethylamine	75-50-3	59.11	–0.38[a]	1630000[a]	–3.720[a]	1.91E-04	1.90E-04	310.42	80	6	EDETOX

[a] Experimental determined data. K_p^{corr} is the corrected K_p calculated using Eq. (5). J_{max} is calculated using Eq. (6). The metabolites of esters, i.e. carboxylic acid and alcohol moieties, are also listed below the parent material shown as italic.

deviation (RMSE) of most water solubility models are between 0.7 and 1.0 **log** units. The reason being that the average uncertainty in measuring water solubility values is no better than 0.6 **log** units (Hewitt et al., 2009; Wang and Hou, 2011). Considering the prediction accuracy of current QSAR models for water solubility, the standard deviation of the four different predictions is added to the average value to give the consensus value used in the calculations for conservative purposes. The final output then converts to the saturated water solubility using Eq. (7) below.

$$C_{water}^{sat}(\mu g/cm^3) = S(mol/L) \times MW(g/mol) \times 1000 \quad (7)$$

Table 3
The seven *in silico* models employed to predict a consensus (average) K_{ow} value when experimental data are lacking.

Prediction model	Molecular descriptor	Modeling method	Training sets		Developer	Remark	Web address/reference
			n	r^2			
AlogPS/VCCLAB	Atom-based	ANN	12908	0.95	VCCL	Free	http://www.vcclab.org/lab/alogps/
AlogP/Pipeline Pilot	Atom-based	MLR	8364	0.90	Accelrys	Commercial	http://accelrys.com/products/pipeline-pilot/
VGlogP/JCHEM	Atom-based	MLR	893	0.93	Chemaxon	Commercial	http://www.chemaxon.com/
XLOGP3	Atom-based	MLR	8199	0.91	SIOC	Free	http://www.sioc-ccbg.ac.cn/?p=42&software=xlogp3
KOWWIN/EPI SUITE	Fragment-based	MLR	2447	0.98	EPA	Free	http://www.epa.gov/opptintr/exposure/pubs/episuite.htm
KLogP/JCHEM	Fragment-based	MLR	1663	0.93	Chemaxon	Commercial	http://www.chemaxon.com/
LogP/MultiCase	Fragment-based	MLR	>8000	0.94	Multicase, Inc.	Commercial	http://www.multicase.com/

All these models calculate K_{ow} based on molecular structure. The training sets of these models cover *MW* ranging from 18 to 992. *n* = number of substances. r^2 = square correlation coefficient.

Table 4
The four *in silico* models employed to predict a consensus (average) water solubility (**log** *S*) value when experimental data are lacking.

Prediction model	Molecular descriptor	Modeling method	Training sets		Developer	Remark	Web address/reference
			n	r^2			
WSKOW/EPI SUITE	Physicochemical property	MLR	1450	0.97	EPA	Free	http://www.epa.gov/opptintr/exposure/pubs/episuite.htm
Solubility/Pipeline Pilot	E-state indices	ANN	1291	0.91	Accelrys	Commercial	http://accelrys.com/products/pipeline-pilot/
KLogS/MultiCase	Fragment-based	MLR	483	0.95	Multicase, Inc.	Commercial	http://www.multicase.com/
XLOGS	Fragment-based	Read-across	4171	0.82	SIOC	Free	http://www.sioc-ccbg.ac.cn/?p=42&software=xlogs

All these models calculate **log** *S* based on molecular structure. The training sets of these models cover *MW* ranging from 27 to 667 and **log** K_{ow}, –8.5 to 10. *n* = number of substances. r^2 = square correlation coefficient.

2.4. Determining the percent skin absorption based on calculated J_{max}

According to Kroes et al., the skin absorption (A) of a material can be estimated based on its calculated J_{max}, as shown in Eq. (8).

$$A(J_{max}) = \begin{cases} 10\%, & J_{max} \le 0.1 \\ 40\%, & 0.1 < J_{max} \le 10 \\ 80\%, & J_{max} > 10 \end{cases} \quad (8)$$

It has been shown that the esters, such as salicylate, readily hydrolyse or metabolize to corresponding carboxylic acid and alcohol on the skin (Belsito et al., 2007). Taking this into consideration, for any ester, the metabolites, which are the carboxylic acid and alcohol, as well as the parent ester, will be processed through the workflow individually in order to obtain their individual J_{max} values. The final J_{max} value to use in assigning a default skin absorption value representative of the ester material will be based on the chemical entity that gave the highest value to err on the conservative side. The overall workflow of conducting skin absorption prediction is depicted in Fig. 1.

2.5. The conservative nature of the calculations

A hallmark of the method employed in this exercise is conservancy. This conservancy is demonstrated in the calculations of **log** K_{ow}, **log** *S* and **log** K_p where multiple models are used to determine a mean value and/or standard error of estimation are incorporated into the calculations. Conservancy is also invoked in the 80, 40 and 10% category cutoff values for percent skin absorption. Specifically, a review of the experimental percent skin absorption values reported in Table 2 reveals that none of the 131 validation materials have skin absorption >80%; in fact, only four materials (i.e., benzyl acetate, benzyl benzoate, carbaryl and cinnamyl alcohol) have skin absorptions > 65%. Additionally, 26 materials exhibit absorption between 65 and 35%, 57 materials exhibit absorption between 35 and 10%, while 44 materials reveal absorptions of <10%.

3. Model validation

3.1. Validation and refinement of Potts and Guy's skin permeability coefficient K_p model

The original equation to predict skin permeability coefficient was developed by Potts and Guy (1992). This model was developed on Flynn's data set with 93 materials which were not entirely composed of fragrance or "fragrance-like" material. Therefore, we questioned the suitability of this model and resolved to tailor it to fit fragrance and "fragrance-like" materials.

One hundred five (105) fragrance and "fragrance-like" materials (i.e., materials with *MW*, **log** K_{ow} and **log** *S* falling into the fragrance chemical space) compose data set I (Table 1). All of them have experimentally determined K_p and **log** K_{ow}. The estimated **log** K_p are calculated using Potts and Guy's equation (Eq. (2)). The square of linear correlation coefficient (r^2) between experimental and estimated **log** K_p is 0.578 with a standard error (SE) of 0.712 (Fig. 3A). Such results indicated that Potts and Guy's equation was acceptable for fragrance materials. However, Potts and Guy's equation was developed for chemicals of diverse structures and functionality in general. Therefore, 105 fragrance and "fragrance-like" materials in data set I were used to re-fit the parameters of Potts and Guy's equation.

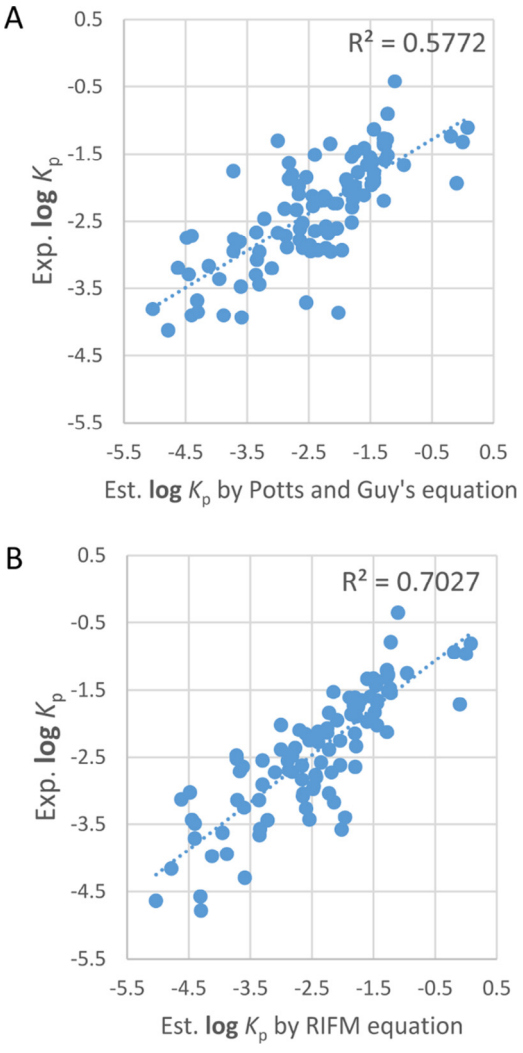

Fig. 3. The correlation of experimental **log** K_p *versus* estimated **log** K_p. (A) Log K_p calculated based on Potts and Guy's equation (Eq. (2)). (B) Log K_p calculated based on Eq. (3).

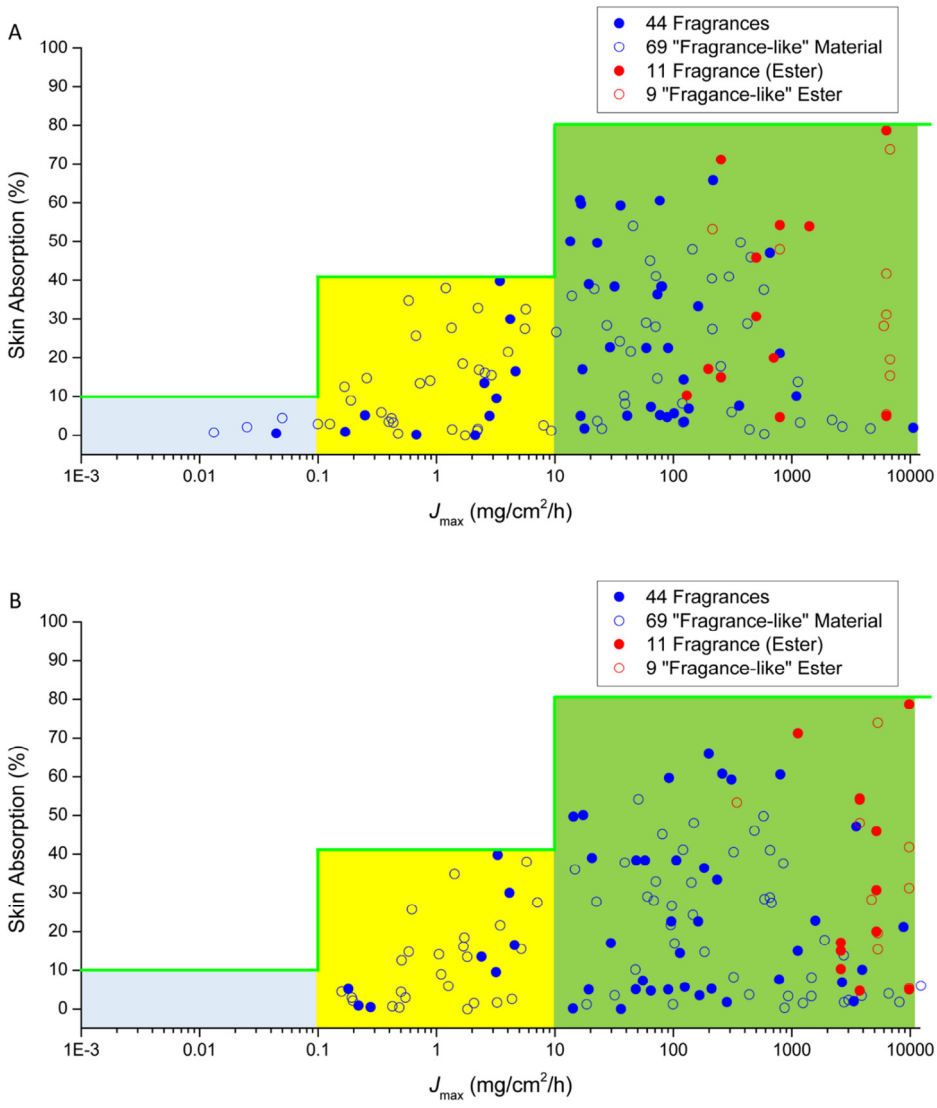

Fig. 4. Plots of calculated J_{max} *versus* experimental percent skin absorption. Shaded areas represent absorption zones (10% (light blue), 40% (yellow), and 80% (green)) from Equation (8). (A) The J_{max} of 131 fragrance (blue and red dots) and "fragrance-like" materials (blue and red circles) were calculated through the workflow depicted in Fig. 1. (B) Assuming there are no experimentally derived parameters available, use consensus values to estimate **log** K_{ow} and **log** S, and using Eq. (4) to calculate the K_p, most of the calculated J_{max} were shifted right.

The updated Eq. (3), namely RIFM's equation, has the r^2 of 0.703 and SE of 0.594 on data set I, which is a fragrance focused data set (Fig. 3B). The higher r^2 value indicates a better fit of Potts and Guy's equation for the fragrance chemical domain. Therefore, RIFM's equation is used to calculate K_p for fragrance and "fragrance-like" materials.

As mentioned above, K_p is not the final output of the SAM. Rather, it is an intermediate parameter used to calculate the J_{max} (see Eq. (1)). Since the conservative estimation is always favorable, we add the standard error of 0.594 of **log** K_p calculated from RIFM's equation as shown in Eq. (4).

3.2. Validation of the SAM

Validation is crucial to prove the suitability and accuracy of a model. The validation data set (data set II) contains 131 fragrance and "fragrance-like" materials, i.e., their *MW*, **log** K_{ow} and **log** S fell within the fragrance defined ranges discussed above, with known experimental skin absorption data (Table 2). The J_{max} was obtained following the workflow described above and as depicted in Fig. 1. The calculated J_{max} values were plotted in relation to the experimental absorption values for these ingredients, as shown in Fig. 4A. The solid blue dots represent the fragrance materials and the blue circles represent the "fragrance-like" materials. Of these 131 materials, 21 were esters (solid red and open red circles). The J_{max} of the esters was obtained as described in section 2.4. By comparing the actual, experimentally derived absorption data with the assigned default values based on J_{max}, one can clearly see that all of the materials fall below the Kroes et al. (2007) predicted default absorption value boundaries. This means the SAM works very well for the materials in our validation set. It is worth noting that all the esters happen to be under the 80% area. This is because we take the metabolites of esters (i.e., carboxylic acid and alcohol moieties) into consideration and choose the most conservative J_{max} to estimate the skin absorption percentage. As mentioned in section 2.2, the validation data set contains data from *in vitro* and *in vivo* data from humans, monkeys and pigs. None of the materials have the experimental determined skin absorption percentage exceeding the

predictions by SAM. This fits the objective of SAM, i.e. giving conservative estimations for human *in vivo* skin absorption instead of using the default value of 100%.

As shown in Fig. 1, when experimentally determined parameters, i.e. **log** K_{ow}, water solubility or K_p are available, those parameters should be used. Our validation data set contained 96 materials with experimentally determined **log** K_{ow}, 82 with experimentally determined water solubility (C_{water}^{Sat}), and 27 had an experimentally determined K_p. Twenty-two (22) had all three parameters experimentally derived (Table 2, marked with [a]). To further test the SAM and understand how skin absorption will map in a case where there are no experimental data available for any of the parameters to calculate J_{max}, we used a predicted **log** K_{ow}, C_{water}^{Sat} and **log** K_p to calculate the J_{max} of our validation set. When we plotted the calculated J_{max} results, most of the materials shifted to the right (Fig. 4B). That is, using all predicted parameter values in one's J_{max} calculation usually results in a more conservative dermal absorption prediction – preferred when experimental data are lacking.

It should be noted that, due to the inherent conservatism built into the SAM by adding the deviation of 0.594 to the calculated **log** K_p and the standard deviation to the average **log** S, there is no need to be extra conservative when dealing with range limit J_{max} values.

3.3. Meeting the OECD principles for QSAR validation

All the QSAR models used in this exercise meets the Organisation for Economic Co-operation and Development (OECD) principles for validation, for regulatory purposes (OECD 2007). Specifically, the models having; 1) a defined endpoint, 2) an unambiguous algorithm, 3) a defined domain of applicability, 4) appropriate measures of goodness-of-fit, robustness and predictivity, and 5) a mechanistic interpretation.

3.4. Applicability domain of the SAM

Our proposed fragrance SAM includes three QSAR models – specifically, **log** K_{ow}, **log** S, and **log** K_p. It is, therefore, necessary to ensure that one's target material falls within the application domain when employing each model. For **log** K_{ow}, the training sets covered materials with molecular weight between 18 and 992 (Table 3). Of these **log** K_{ow} models, four models were trained by a data set containing more than 8000 materials. For example, the training set of AlogPS contains almost 13,000 structurally diverse materials and covers the fragrance chemical space. The final **log** K_{ow} is the average value of these seven models. For the 105 fragrance and "fragrance-like" materials in the data set I, the squared correlation coefficient (r^2) of the experimental and estimated **log** K_{ow} are 0.97, and the root-mean-square deviation (RMSE) is 0.25. This means that the consensus **log** K_{ow} model works very well with fragrance materials.

The training sets for **log** S models covered materials with molecular weight from 27 to 667 and **log** K_{ow} from –8.5 to 10 (Table 2). The fragrance chemical space is also covered by these training sets. However, the number of materials in each training set is comparably less than those of **log** K_{ow} models. The largest training set is that of XLOGS, which contains 4171 compounds with known **log** S values. The r^2 and RMSE in regression were 0.82 and 0.96 **log** units, respectively (Duan et al., 2012). As discussed above, the uncertainty of the water solubility is significant in experiments. The prediction models usually have high RMSE. Therefore, the estimated **log** S from our model was added by the standard deviations from different prediction models for conservative purpose.

K_p was calculated based on RIFM's equation (Eq. (3)), which is an updated formula from Potts and Guy's equation (Eq. (2)). The training set (data set I) contains 105 fragrance and "fragrance-like" materials, which makes it a fragrance focused model. The **log** K_p model covered materials with MW from 33 to 330 and **log** K_{ow} from –1 to 6.

If the target material falls into these training set ranges, it is considered to be in the fragrance application domain and therefore suitable for processing, as we have described. If the target material does not fall into this application domain, it may still be processed but a low confidence caution should be given (i.e., Low Confidence Warning in Fig. 1).

4. Application of the SAM in safety assessment

We have demonstrated that the SAM is sound to use when experimental skin absorption data are lacking and thus, we propose using the outcomes of this semi-quantitative, mechanistic, *in silico* model instead of the unreasonable 100% default in cases where it will make a difference in thresholds like TTC (Threshold of Toxicological Concern) and MOE or MOS (margin of exposure or margin of safety) (Eaton and Gilbert, 2007; Kroes et al., 2005, 2007).

To demonstrate this, consider the following hypothetical example. Material "X," that meets the above described criteria (see section 2.1), does not have animal data or suitable analogs for read-across to clear it for the toxicity endpoint of interest. The material is used at very low levels and its TTC of 30 μg/kg/day (based on a Cramer Class I material) is considered. The total systemic exposure, based on the default assumption of 100% skin absorption, is 34 μg/kg/day. These values are so close that a more representative percent absorption may bring the total systemic exposure below the TTC leading to different risk management. The following steps are taken to calculate absorption based on J_{max}:

1. Get the MW (g/mol), and check for experimentally determined parameters of K_p (cm/h), C_{water}^{sat} (mg/L), and **log** K_{ow}. In this case, we know the structure and the MW = 204 g/mol but have no other experimental values.
2. Determine **log** K_{ow} by calculating it from the seven *in silico* tools of Table 1.

log K_{ow} model	Result
KOWWIN/EPI SUITE	5.48
AlogP/Pipeline Pilot	4.18
VGlogP/JCHEM	3.98
KLogP/JCHEM	4.27
LogP/MultiCase	4.22
XLOGP3	5.08
AlogPS/VCCLAB	4.65
Average ± STD	4.55 ± 0.55

3. Calculate K_p (cm/h) by using Eq. (4). That is, **log** K_p (cm/h) = –1.356 + 0.759 × **log** K_{ow} – 0.0118 × MW = –1.356 + (0.759 × 4.55) – (0.0118 × 204.36) = –0.314. Note that the deviation of 0.594 has been added to the calculated **log** K_p for conservative purposes. Therefore, $K_p = 10^{\log Kp} = 10^{-0.314} = 0.485$ cm/h.
4. Correct the K_p by using Cleek and Bundge's equation (Eq. (5)):

$$Kpcorr = Kp \Big/ \left(1 + \frac{Kp\sqrt{MW}}{2.6}\right) = 0.485 \Big/ \left(1 + \frac{0.485 \times \sqrt{204.36}}{2.6}\right) = 0.132\ \text{cm/h}.$$

5. Derive water solubility (C_{water}^{Sat}) by determining it from the four *in silico* tools of Table 3.

log S model	Result
WSKOW/EPI SUITE	–5.91
Solubility/Pipeline Pilot	–4.48
KLogS/MultiCase	–4.30
XLOGS	–4.25
Average ± STD	–4.73 ± 0.79

This water solubility is used to calculate J_{max}. For conservative purposes, the standard deviation is added to the average **log** *S*: –4.73 + 0.79 = –3.94. S = 10 × **log** *S* = 10 – 3.94 = 0.000114 mol/L. *S* is converted to $C_{water}^{Sat} = S \times MW \times 1000 = 0.000114 \times 204.36 \times 1000 = 23.29\ \mu g/cm^3$.

6. Calculate J_{max} as follows: $J_{max} = K_p^{corr} \times C_{wat}^{sat} = 0.132 \times 23.29 = 3.07\ \mu g/cm^2/h$. According to Eq. (8), the 40% estimated percent skin absorption is assigned to this material. By assigning 40% absorption, the systemic exposure becomes 15.22 μg/kg/day, which is approximately twofold below its determined TTC and now clears the toxicological endpoint of interest.

This example demonstrates the unreasonableness of defaulting to 100% skin absorption when experimental data are lacking and the usefulness of this model in calculating more representative percent absorption values for fragrance or "fragrance-like" materials.

It is worth noting that even though this example uses seven different **log** K_{ow} prediction models and four different water solubility models to obtain the consensus estimated **log** K_{ow} and water solubility values, one does not have to use as many – one may even use other validated models to get a consensus estimation. For example, if only the three free accessible **log** K_{ow} models (i.e. KOWWIN, XlOGP3 and ALOGPS) and two free accessible water solubility models (WSKOW and XLOGS) are used, the final conclusion would not change (J_{max} = 4.00 μg/cm²/h, in 40% absorption range).

5. Conclusion

We concur with Kroes et al.'s (2007) assumption that 100% skin absorption is not a scientifically supportable default value in the absence of experimental data. Furthermore, we showed that Kroes et al.'s three tier percent skin absorption scheme for cosmetic ingredients fit very well for fragrance ingredients. We developed a specific skin absorption model, namely SAM, for fragrance ingredients whose default absorption value is either 10, 40, or 80%. To which percent absorption domain a fragrance ingredient falls depends on its calculated J_{max}. Our *in silico* model was validated using 131 fragrance materials with experimental *in vitro* or *in vivo* absorption data obtained from either human or pig skin. Although the SAM deviates from the 100% default absorption value, it still has a lot of conservatism built into it. A schematic of the SAM is shown in Fig. 1 and an example of how to use the model is discussed in Section 4. This model is very useful in prioritizing testing, when the estimated exposure is very close to TTC, or when it will make a significant difference in estimating the point of departure.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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