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Review

Calculating the dermal flux of chemicals with OELs based on their molecular structure: An attempt to assign the skin notation

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ABSTRACT

Our objectives included calculating the permeability coefficient and dermal penetration rates (flux value) for 112 chemicals with occupational exposure limits (OELs) according to the LFER (linear free-energy relationship) model developed using published methods. We also attempted to assign skin notations based on each chemical's molecular structure. There are many studies available where formulae for coefficients of permeability from saturated aqueous solutions (K_p) have been related to physicochemical characteristics of chemicals. The LFER model is based on the solvation equation, which contains five main descriptors predicted from chemical structure: solute excess molar refractivity, dipolarity/polarisability, summation hydrogen bond acidity and basicity, and the McGowan characteristic volume. Descriptor values, available for about 5000 compounds in the Pharma Algorithms Database were used to calculate permeability coefficients. Dermal penetration rate was estimated as a ratio of permeability coefficient and concentration of chemical in saturated aqueous solution. Finally, estimated dermal penetration rates were used to assign the skin notation to chemicals. Defined critical fluxes defined from the literature were recommended as reference values for skin notation. The application of Abraham descriptors predicted from chemical structure and LFER analysis in calculation of permeability coefficients and flux values for chemicals with OELs was successful. Comparison of calculated K_p values with data obtained earlier from other models showed that LFER predictions were comparable to those obtained by some previously published models, but the differences were much more significant for others. It seems reasonable to conclude that skin should not be characterised as a simple lipophilic barrier alone. Both lipophilic and polar pathways of permeation exist across the stratum corneum. It is feasible to predict skin notation on the basis of the LFER and other published models; from among 112 chemicals 94 (84%) should have the skin notation in the OEL list based on the LFER calculations. The skin notation had been estimated by other published models for almost 94% of the chemicals. Twenty-nine (25.8%) chemicals were identified to have significant absorption and 65 (58%) the potential for dermal toxicity. We found major differences between alternative published analytical models and their ability to determine whether particular chemicals were potentially dermotoxic.

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1. Introduction

The concept of skin notation is used as a tool to identify potential health risks related to transdermal penetration of a chemical with known admissible levels of occupational exposure. The strategy for assigning the skin notation to chemicals is based on various quantitative and qualitative criteria. The usual practice is to adopt the median lethal dose (LD_{50}) when the chemical is applied to the skin of experimental animal, to provide the skin notation (Scansetti et al., 1988; Kennedy et al., 1993). Classification and labelling of chemicals in the European Union List of hazardous substances, from the point of view of their skin contact toxicity, according to the numeric criteria expressed as LD_{50} dermal values, may be helpful for assessing their skin absorption (CLP, 2008). Proofs of significant dermal absorption rates may be obtained from experiments in vitro, experiments using intact animals or human results. Some countries also include skin irritation and dermatoses as a reason for assigning the skin notation on chemicals.

Accessibility of experimental data on dermal chemical uptake is limited in the scientific literature and besides, several reports feature different data on skin absorption for the same chemical. There are significant differences in measurements among animal species and among measurements obtained by chemically exposing skin from different parts of the body. The outcome of the measurements also depends on the form in which chemical is applied, on the concentration and solubility of the chemical in the vehicle, and on the effects of the vehicle on the physiological status of the skin. Since dermal absorption is a kinetic process, the outcome of the measurements depends on exposure duration and sampling time. The European regulatory risk assessors showed that there were no reliable databases for skin permeation in vitro or in vivo. Nevertheless, a database of validated skin permeation coefficients collected a comprehensive data set containing 186 permeability coefficients for some 158 structurally diverse compounds (Vecchia and Bunge, 2002; Patel et al., 2002). The EDETOX database also brought together in vivo and in vitro percutaneous absorption and distribution data from all available sources, together with the physicochemical data for each chemical of interest (WHO, 2006). Flynn (1990) published a set of permeability coefficients for 97 compounds.

When relevant data is not available, mathematical modelling is used to predict the amount of a substance permeating through the skin. Theoretical models relate flux to the diffusibility of chemicals through a hypothetical reference skin, the parameters of which (thickness, diffusion channels, and diffusion constant) are compiled as mean values for human skin. Several mathematical models have been applied for the estimation of dermal absorption from exposure to chemicals. There are several studies (Brown and Rossi, 1989; Fiserova-Bergerova et al., 1990; McKone and Howd, 1992; Robinson, 1993; Potts and Guy, 1993; Wilschut et al., 1995) in which expressions for permeability coefficient from saturated solution in water (K_p) have been related to physicochemical properties of chemicals.

The key descriptors for controlling the penetration ability of a compound are hydrophobicity, molecular size and hydrogen bonding ability. Fiserova-Bergerova et al. (1990) presented algorithms predicting the dermal flux of industrial nonelectrolyte chemicals (known as the FB model). They chose to use a parallel, two-pathway skin penetration model (Berner and Cooper, 1987) for the evaluation of the permeability coefficient (K_p). In this approach, it is assumed that both lipophilic and polar pathways of permeation exist across the stratum corneum (SC) and that K_p can be expressed by equation:

$$K_p = \frac{A_p D_p + A_L D_L}{h} \quad (1)$$

where A_p and A_L denote the area fractions of polar and lipid pathways, respectively, and D_p and D_L are the corresponding permeant diffusion coefficients for the two routes, and h is the thickness of the SC. In this model, $A_p = 0.1$, $A_L = 0.9$ and $h = 15$ μm. The diffusion coefficients were calculated from free-volume theory, which predicts that D_p and D_L will decrease exponentially with increasing permeant molecular weight (MW):

$$K_p = [0.0025 + 0.0102 K_{ow}] \ \exp(-0.016 \ MW) \quad (2)$$

where K_p is the penetrant's permeability coefficient (cm/h); K_{ow} is the octanol/water partition coefficient; MW is the molecular weight.

The Potts and Guy (1993) approach (known as PG model) is different than that of Berner and Cooper (1987). Skin is characterised as a simple lipophilic barrier alone. The starting point was simple definition of K_p:

$$K_p = D\frac{K}{\delta} \quad (3)$$

where D is the penetrant's diffusion coefficient in the stratum corneum; K, is stratum corneum water partition coefficient; and δ is the diffusion path length across the stratum corneum.

They also used free-volume theory to relate D to MW and, on the basis of experimental data, to relate K to P. Multiple regression of the literature K_p values on K_{ow} and MW resulted in the following equation:

$$\text{Log} \ K_p = -2.74 + 0.71 \ \text{Log} \ K_{ow} - 0.0061 \ MW \quad (4)$$

where Log K_p is decimal logarithm.

The FB model was found to be conservative by Potts and Guy (1993) because it always predicted a higher K_p than that of Potts and Guy (1993). The magnitude of the difference is greatest for very small and very large values of Log K_{ow}. The obtained ratios of predicted percutaneous fluxes were substantial and ranged from 2.1 to 120 times.

The European regulatory risk assessors tried to derive a QSAR for estimation of the skin permeation coefficient through human skin in vitro. The general QSAR based on Flynn dataset has the form based on Potts and Guy (1992) but further improved to maximise the quality (Patel et al., 2002).

$$\text{Log} \ K_p = 0.781 \ \text{Log} \ K_{ow} - 0.01115 \ MW - 2.19 \quad (5)$$

NIOSH U.S. (2009) proposed the skin permeation calculator in the internet based on Flynn dataset, Potts and Guy's model and Robinson's model.

Estimated dermal penetration rates were used to assign the skin notation to chemicals with known admissible levels of occupational exposure. Fiserova-Bergerova et al. (1990) proposed the complex criteria for skin notation in occupational settings and created the philosophy which allowed the predicting of skin notation of chemicals for which occupational exposure limits (OELs) have been determined. They defined critical fluxes (Fl* and Fl** in mg/cm^2/h) which were recommended as reference values for skin notation. Critical flows depend on the highest admissible concentration of the chemical in ambient air obtained from Eqs. (6) and (7):

$$Fl* = 0.75 \ OEL \quad (6)$$

$$Fl** = 5 \ OEL \quad (7)$$

where OEL is the corresponding occupational limit value in the work environment.

According to Fiserova-Bergerova et al. (1990) approach, the effect of dermal absorption of occupationally relevant chemical compounds will be evaluated at two biologically significant levels:

(1) the dermal absorption potential will be considered to be significant if the dermal penetration rate of nonvolatile chemicals exceeds 30% of the pulmonary uptake rate during an occupational inhalation exposure to OEL, or if dermal absorption of volatile chemicals increases the arterial blood concentration 30% above the concentration most likely reached during occupational inhalation exposure to OEL; and (2) potential for systemic toxicity induced by dermal exposure will be considered significant if the biological levels triple compared with the biological levels resulting from inhalation exposure to OEL. The chemical should carry a skin notation if the potential for dermal absorption and toxicity is significant. Fiserova-Bergerova et al. considered the following criteria for *skin notation* of chemicals in the OEL list should be adopted, using the specified reference values of Fl* and Fl**:

1. If absorption of a chemical through 2% body surface results in 30% increase of the biological level of the chemical, i.e. when Fl* < Fl (Fl*/Fl < 1), then the chemical should be classified as probably absorbable through the skin, and ought to be provided with the suitable notation in the OEL list.
2. If absorption of a chemical through 2% body surface results in threefold increase of the biological level of the chemical (increase by 200%), i.e. when Fl** < Fl (Fl**/Fl < 1) or Fl*/Fl = 0.15, then the chemical should be classified as absorbable through the skin, and ought to be provided with the suitable notation in the OEL list.

Abraham (1993) developed the general equation that seems satisfactory for explaining dermal absorption as kinetic process. The LFER model for predicting the Log K_p values (ABR model) is based on the solvation equation, or linear free-energy relationship which contains five main descriptors predicted from chemical structure (Abraham and Martins, 2004):

$$SP = c + eE + sS + aA + bB + Vv \quad (8)$$

The dependent variable in this equation is a property of a series of solutes in a given system. SP can be Log K_p or can be some physicochemical property. The independent variables are solute descriptors as follows (Abraham, 1993; Abraham et al., 1999):

E is the solute excess molar refractivity in units of $(cm^3\ mol^{-1})/10$. Molar refractivity is a measure of the volume occupied by an atom or group and is dependent on the temperature, the index of refraction, and the pressure. It is the volume of the substance taken up by each mole of that substance.

S is the solute dipolarity/polarizability. Polarizability is the relative tendency of the electron cloud of an atom to be distorted from its normal shape by the presence of a nearby ion or dipole – that is, by an external electric field.

A and *B* are the overall or summation hydrogen bond acidity and basicity. Hydrogen bond is a type of attractive intermolecular force that exists between two partial electric charges of opposite polarity.

V is the McGowan characteristic volume unit of $(cm^3\ mol^{-1})/100$. The McGowan volume is calculated from the individual atomic sizes and number of bonds in each molecule (Abraham and McGowan, 1987).

Descriptors are derived from free-energy related properties. The coefficients in Eq. (8) are obtained by multiple linear regression analysis.

The equation is expected to predict Log K_p to 0.5 units.

$$\text{Log } K_p(\text{water} - \text{skin permeation in cm}/s) = -5.426 - 0.106E - 0.473S - 0.473A - 3B + 2.296V \quad (9)$$

Hence, the aim of this work is to apply a modern model based on the linear free-energy relationship equation to calculate the permeability coefficients and flux values (dermal penetration rates) for occupationally relevant chemicals absorbed through the skin. Because to the great practical importance of the skin notation for substances included in the lists of occupational exposure limits, we have attempted to apply estimated dermal penetration rates to assign the skin notation to chemicals with known admissible levels of occupational exposure. We have used the Fiserova-Bergerova et al. guidelines on dermal absorption of occupationally relevant chemical compounds to obtain critical flux as the reference values for skin notation. We performed studies to determine if the FB model was still applicable in this context.

2. Methods

The salvation equation (9) was applied to calculate the permeability coefficient values (K_p) according to LFER model (ABR model). The compound descriptors were obtained from the software package Pharma Algorithms (2008). Descriptor values are available for about 5000 compounds in this database.

Next, dermal penetration rate or flux through the skin (Fl) was obtained through multiplying the permeation coefficient and the concentration of chemical in saturated aqueous solution (C_{sat}) according to Eq. (10):

$$Fl = K_p C_{sat} \quad (10)$$

The dataset used here is the same as that introduced by Fiserova-Bergerova et al. (1990).

Calculation of permeability coefficient values and fluxes was attempted for 132 chemicals analysed by Fiserova-Bergerova et al. (1990), but some compounds were excluded because relevant data was not available in the Pharma Algorithms database. Thus, finally we chose 112 (54 volatile and 58 nonvolatile) chemicals. The skin notation had been previously estimated by Fiserova-Bergerova et al. (1990) for almost 94% of these. Thirty four percent have been assigned the skin notation in the ACGIH 2009 list. For the remaining chemicals, the scientific basis was not sufficiently strong to assign skin notation. The full list of the compounds used in the study is shown in Table 1.

Finally, we applied estimated dermal penetration rates to assign the skin notation to chemicals with known admissible levels of occupational exposure, according to the complex criteria for skin notation developed by Fiserova-Bergerova et al.:

- An increase of the biological level above the no effect level was considered to be a critical effect.
- Blood concentration resulting from occupational inhalation exposure to OEL–TWA (threshold weighted average) was considered as the no effect level
- The dermal absorption potential is significant if dermal absorption increases the arterial blood concentration 30% above the concentration reached during exposure to OEL–TWA.
- Potential for systemic toxicity induced by dermal exposure is significant if biological levels triple biological levels resulting from inhalation exposure to OEL–TWA.

The critical flux (Fl*) was calculated as a fraction of occupational exposure limit based on a simple Eq. (6). If Fl*/Fl < 1, then the chemical should be provided with the suitable notation in the OEL list. The values of the occupational exposure limit are given in the ACGIH guide to occupational exposure values (2009) (Table 1).

Statistical analysis was carried out using independent groups *t*-test for means to compare the means of two independent groups.

3. Results and discussion

Table 1 lists 112 chemicals for which occupational exposure values have been determined, together with:

- fluxes (Fl, mg/cm^2/h) and permeability coefficient values (Log K_p cm/h), calculated from the Abraham and Martins (2004) model
- critical fluxes (Fl*, mg/cm^{2}h) and the critical flux to calculated flux (Fl*/Fl) ratio
- occupational exposure levels obtained as threshold limit values (TLV, mg/l) from ACGIH guide (2009)
- Chemicals which should be provided with the suitable notation about skin absorption in the OEL list according to LFER model and Fiserova-Bergerova et al. approach were shown in Table 2. Nonvolatile and volatile chemicals identified by ABR model to have significant absorption (0.15 < Fl*/Fl < 1)) or the potential for dermal toxicity (Fl*/Fl < 0.15) were submitted. From among 112 chemical 94 should have the *skin notation* in the OEL list and

Table 1
112 chemicals for which occupational exposure values have been determined, together with fluxes (Fl, mg/cm^2/h) and permeability coefficient values (Log K_p cm/h), calculated from the l, critical fluxes (Fl*, mg/cm^{2}h) and the critical flux to calculated flux (Fl*/Fl) ratio.

Chemical	CAS No.	OEL [mg/l]	Fl* [mg/cm^2/h]	Log K_p ABR [cm/h]	Fl ABR [mg/cm^2/h]	Fl*/Fl
Acetic acid	64-19-7	0.0250	0.0188	−2.4586	3.6490	0.0051
Acetone	67-64-1	1.1880	0.8910	−1.9740	8.2600	0.1079
Acetonitrile	75-05-8	0.0340	0.0255	−1.9024	9.8031	0.0026
Acetylsalicylic acid	50-78-2	0.0050	0.0038	−2.2530	0.0558	0.0671
Allylalcohol	107-18-6	0.0012	0.0009	−2.1166	6.5292	0.0001
2-Aminopyridine	504-29-0	0.0020	0.0015	−2.6956	0.1109	0.0135
n-Amyl acetate	628-63-7	0.5250	0.3938	−0.6667	0.4309	0.9139
Aniline	62-53-3	0.0076	0.0057	−1.9965	0.3428	0.0166
Atrazine	1912-24-9	0.0050	0.0038	−1.7037	0.0014	2.7079
Benzene	71-43-2	0.0016	0.0012	−0.9706	0.1905	0.0063
1.3-Butadiene	106-99-0	0.0044	0.0033	−1.1122	0.0568	0.0581
n-Butanol	71-36-3	0.0610	0.0458	−1.5070	2.3960	0.0191
n-Butyl acetate	105-46-4	0.7100	0.0083	−0.9039	1.7467	0.3049
n-Butyl acrylate	141-32-2	0.0110	0.0413	−0.5767	0.4241	0.0195
n-Butylamine	109-73-9	0.0150	0.0113	−2.1942	4.6871	0.0024
Sec. butanol	78-92-2	0.3050	0.2288	−1.2651	6.7891	0.0337
Chlorobenzene	108-90-7	0.0460	0.0345	−0.7122	0.0970	0.3557
Chloroform	67-66-3	0.0500	0.0375	−0.7736	1.3727	0.0273
Chloropicrine	76-06-2	0.0007	0.0005	−1.0562	0.1757	0.0030
o-Cresol	108-39-4	0.0220	0.0165	−1.6610	0.5457	0.0302
m-Cresol	95-48-7	0.0220	0.0165	−1.6610	0.5129	0.0322
p-Cresol	106-44-5	0.0220	0.0165	−1.6610	0.5239	0.0315
Cumene	98-82-8	0.2450	0.1838	−0.0649	0.0431	4.2673
Cyclohexane	110-82-7	0.3440	0.7875	−0.1434	0.0395	6.5261
Cyclohexanol	108-93-0	0.2000	0.1500	−1.1939	2.3036	0.0651
Cyclohexanone	108-94-1	0.0500	0.0375	−1.2613	1.2602	0.0298
Cyclohexene	110-83-8	1.0100	0.2580	−0.4580	0.0742	10.2094
o-Dichlorobenzene	95-50-1	0.1500	0.1125	−0.4528	0.0353	3.1912
p-Dichlorobenzene	106-46-7	0.0600	0.0600	−0.4702	0.0268	1.6818
Dichloroethyl ether	111-44-4	0.0300	0.0225	−0.7024	2.0240	0.0111
Dieldrin	60-57-1	0.0001	0.0001	0.0629	0.2254	0.0003
Diethanolamine	111-42-2	0.0010	0.0008	−4.1497	0.0676	0.0111
Diethyl ketone	96-22-0	0.7050	0.5288	−1.3237	2.2305	0.2371
2-Diethylaminoethanol	100-37-8	0.0096	0.0072	−2.4720	2.9850	0.0024
Diisopropylamine	108-18-9	0.0200	0.0150	−1.3058	0.3956	0.0379
N.N-dimethyl aniline	121-69-7	0.0250	0.0188	−1.2429	0.0640	0.2929
Dimethyl phthalate	131-11-3	0.0050	0.0038	−1.6593	0.1096	0.0342
N.N-Dimethylacetamide (DMAC)	127-19-5	0.0350	0.0263	−2.5175	2.8643	0.0092
Dimethylformamide (DMF)	68-12-2	0.0300	0.0225	−2.8368	1.3746	0.0164
Dioxane	123-91-1	0.0720	0.0540	−1.9312	12.1033	0.0045
Diphenylamine	122-39-4	0.0100	0.0075	−0.7338	0.0554	0.1354
Diuron	330-54-1	0.0100	0.0075	−1.6359	0.0010	7.7216
Enflurane	13838-16-9	0.5750	0.4313	−0.6858	2.0616	0.2092
Ethanol	64-17-5	1.9000	1.4250	−2.1503	5.5819	0.2553
Ethanolamine	141-43-5	0.0080	0.0060	−4.0321	0.0945	0.0635
2-Ethoxyethanol	110-80-5	0.0190	0.0143	−2.3154	4.5035	0.0032
Ethyl acetate	141-78-6	1.4000	1.0500	−1.5173	2.6438	0.3972
Ethyl benzene	100-41-4	0.4350	0.3263	−0.3020	0.0998	3.2698
Ethyl ether	60-29-7	1.2000	0.9000	−1.1066	5.3982	0.1667
Ethyl formate	109-94-4	0.3000	0.2250	−1.8065	1.7175	0.1310
Ethyl mercaptane	75-08-1	0.0010	0.0008	−1.2417	0.5732	0.0013
Ethylamine	75-04-7	0.0092	0.0135	−2.8076	1.0653	0.0127
Ethylchloride	75-00-3	0.2640	0.1980	−0.9475	1.1285	0.1755
Ethylene glycol	107-21-1	0.1000	0.0750	−3.0785	0.9290	0.0807
Formaldehyde	50-00-0	0.0004	0.0011	−2.5047	0.9385	0.0012
Formamide	75-12-7	0.0150	0.0113	−3.5304	0.3341	0.0337
Formic acid	64-18-6	0.0090	0.0068	−2.7537	2.1511	0.0031
Furfural	98-01-1	0.0080	0.0060	−2.1638	0.5692	0.0105
Glycerin	56-81-5	0.0100	0.0075	−3.8221	0.1904	0.0394
Halothane	151-67-7	0.4000	0.3000	−0.3971	1.8035	0.1663
n-Heptane	142-82-5	1.6000	1.2000	0.3996	6.0230	0.1992
Hexachloroethane	67-72-1	0.0100	0.0075	−0.1783	0.0332	0.2261
n-Hexane	110-54-3	0.1800	0.1350	0.1108	0.0181	7.4714
Hexylene glycol	107-41-5	0.1250	0.0938	−2.0376	8.4646	0.0111
Isoamyl alcohol	123-51-3	0.3600	0.2700	−1.2650	1.6298	0.1657
Isobutyl alcohol	76-83-1	0.1500	0.1125	−1.5923	2.4290	0.0463
Isopropyl alcohol	67-63-0	0.4920	0.3690	−1.9084	9.6933	0.0381
Lindane	58-89-9	0.0005	0.0004	−0.1091	0.0132	0.0284
Mesityl oxide	141-79-7	0.0600	0.0450	−1.4144	1.0784	0.0417
Methanol	67-56-1	0.2600	0.1950	−2.4391	2.8779	0.0678
Methoxychlor	72-43-5	0.0100	0.0075	0.7256	0.2126	0.0353
Methyl acetate	79-20-9	0.6100	0.4575	−1.8360	4.6536	0.0983
Methyl chloride	74-87-3	0.1050	0.0788	−1.2662	4.7674	0.0165

Table 1 (*Continued*)

Chemical	CAS No.	OEL [mg/l]	Fl* [mg/cm²/h]	Log K_p ABR [cm/h]	Fl ABR [mg/cm²/h]	Fl*/Fl
Methyl chloroform	71-55-6	1.9000	1.4250	−0.4012	1.7468	0.8158
Methyl ethyl ketone	78-93-3	0.5900	0.4425	−1.6505	7.8936	0.0561
Methyl iodide	74-88-4	0.0100	0.0075	−1.1373	1.3121	0.0057
Methyl isobutyl ketone	108-10-1	0.2050	0.1538	−1.0937	1.5313	0.1004
Methyl propyl ketone	107-87-9	0.5290	0.3968	−1.3307	2.0080	0.1976
Methylal	109-87-5	3.1000	2.3250	−2.0005	3.2962	0.7054
Methylamine	74-89-5	0.0064	0.0048	−3.1311	0.8969	0.0054
Methylene chloride	75-09-2	0.1750	0.1313	−0.9804	2.0923	0.0627
Metribuzin	21087-64-9	0.0050	0.0038	−3.5675	0.0003	11.5438
Morpholine	110-91-8	0.0700	0.0525	−2.5999	2.5301	0.0208
Naphthalene	091-20-3	0.0500	0.0375	−0.5047	0.0094	3.9958
p-Nitroaniline	100-01-6	0.0030	0.0023	−2.2184	0.0048	0.4650
Nitromethane	75-52-5	0.0500	0.0375	−1.9771	1.1279	0.0332
p-Nitrotoluene	99-99-0	0.0110	0.0083	−0.7891	0.0715	0.1154
Pentachlorophenol (PCP)	87-86-5	0.0005	0.0004	0.3149	0.0021	0.1816
Pentaerythritol	115-77-5	0.0100	0.0075	−4.2510	0.0031	2.4043
Phenyl ether	101-84-8	0.0070	0.0053	−0.6420	0.0048	1.0963
p-Phenylene diamine	106-50-3	0.0001	0.0001	−3.0329	0.0385	0.0019
Propoxur	114-26-1	0.0005	0.0004	−1.5826	0.0523	0.0072
n-Propyl acetate	109-60-4	0.8400	0.6300	−1.2238	1.1289	0.5581
n-Propyl alcohol	71-23-8	0.2460	0.1845	−1.8268	7.5248	0.0245
Propylene dichloride	78-87-5	0.0460	0.0345	−0.7404	0.4909	0.0703
Ronnel	299-84-3	0.0050	0.0038	−0.5772	0.0106	0.3541
Strychnine	57-24-9	0.0002	0.0002	−2.5969	0.0004	0.4146
Styrene	100-42-5	0.0850	0.0638	−0.5919	0.0768	0.8303
Thioglycolic acid	68-11-1	0.0040	0.0030	−2.5556	3.6865	0.0008
Toluene	108-88-3	0.0750	0.0563	−0.6208	0.1437	0.3915
o-Toluidine	95-53-4	0.0090	0.0068	0.9333	128.6453	0.0001
p-Toluidine	106-49-0	0.0090	0.0068	−1.6467	0.1669	0.0404
Tributyl phosphate	126-73-8	0.0025	0.0019	−0.8465	0.8401	0.0022
Trichloroacetic acid	76-03-9	0.0070	0.0053	−1.8628	0.1783	0.0294
1.2.4-Trichlorobenzene	120-82-1	0.0400	0.0300	−0.0229	0.0180	1.6644
1.1.2-Trichloroethane	79-00-5	0.0550	0.0338	−0.8112	0.6950	0.0486
Trichloroethylene	79-01-6	0.0540	0.0405	−0.9147	0.1339	0.3025
Trichlorofluoromethane	75-69-4	5.6000	4.2000	−0.6285	0.2588	16.2313
Triethylamine	121-44-8	0.0041	0.0031	−1.2332	0.8768	0.0035
o-Xylene	95-47-6	0.4350	0.3263	−0.2768	0.0952	3.4283
m-Xylene	108-38-3	0.4350	0.3263	−0.2768	0.0952	3.4283
p-Xylene	106-42-3	0.4350	0.3263	−0.2768	0.1057	3.0854

Table 2
Chemicals which should have the skin notation In the MAC LIST, identified by the model of Abraham and Martins (2004).

Chemicals to have significant absorption (0.15 < Fl*/Fl < 1)			
Acetone	n-Amyl acetate	n-Butyl acetate	Chlorobenzene
Diethanolamine	Diethyl ketone	N,N-Dimethylaniline	Enflurane
Ethanol	Ethyl acetate	Ethyl chloride	ethyl ether
Halothane	n-Heptane	Hexachloroethane	isoamyl alcohol
Methylal	Methyl chloroform	Methyl propyl ketone	p-nitroaniline
Nitromethane	PCP	n-Propyl acetate	Propylene dichloride
Ronnel	Strychnine	Styrene	Toluene
Trichloroethene			
Chemicals to have toxicity potential (Fl*/Fl < 0.15)			
Acetic acid	Acetonitrile	Acetylsalicylic acid	allylalcohol
2-Aminopyridine	Aniline	Benzene	butadiene
n-Butanol	Sec. butanol	n-Butyl acrylate	n-Butylamine
Chloroform	Chloropicrine	o-Cresol	m-Cresol
p-Cresol	Cyclohexanole	Cyclohexanone	Dichloroethyl ether
Dieldrin	2-Diethylamonoethanol	Diisopropylamine	Dimethyl phthalate
DMAC	DMF	Dioxane	Diphenylamine
Ethanolamine	2-Ethoxyethanol	Ethylamine	Ethylene glycol
Ethyl formate	Ethyl mercaptane	Formaldehyde	Formamide
Formic acid	Furfural	Glycerin	Hexylene glycol
Isobutyl alcohol	Isopropyl alcohol	Lindane	Mesityl oxide
Methanol	Methoxychlor	Methyl acetate	Methylamine
Methyl chloride	Methylene chloride	Methyl ethyl ketone	Methyl iodide
Methyl isobutyl ketone	Morpholine	p-Nitrotoluene	p-Phenylene diamine
propoxur	n-Propyl alcohol	Thioglycolic acid	o-Toluidine
p-Toluidine	Tributyl phosphate	Trichloroacetic acid	1,1,2-Trichloroethane
Triethylamine			

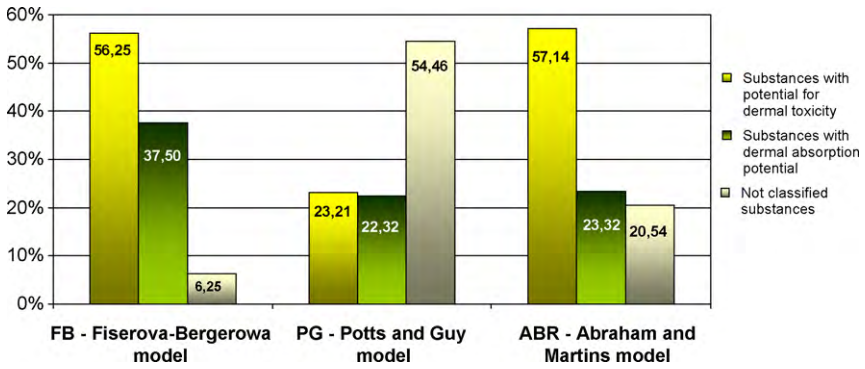

Fig. 1. Chemicals with potential for dermal toxicity or dermal absorption potential.

18 should not. 29 chemicals were identified to have significant absorption and 65 the potential for dermal toxicity.

The LFER method was confirmed using FB model. Eq. (3) was used to calculate K_p values according to FB method. For modelling studies, a number of data sets, for example the critical flux and other flux values, were compiled from Fiserova-Bergerova et al. (1990) study. A dataset consisting of physicochemical properties of 112 chemicals was obtained from the same paper. Potts and Guy (1993) considered the same chemicals for the *skin notation*. We used Eq. (4) to predict permeability coefficients by PG method. Finally, the permeability coefficient values predicted by chosen models were compared. Out of the 71 nonvolatile chemicals, Potts and Guy found 21 chemicals with potential for dermal toxicity, another 13 with potential for absorption alone, and 37 without significant permeability, while the corresponding numbers suggested by Fiserova-Bergerova et al. were 48, 21 and 2, respectively. Of the 60 volatile compounds, Potts and Guy found 13 with dermal toxicity (vs. 29 suggested by Fiserova-Bergerova et al.), 15 with dermal absorption potential (vs. 26), and 33 without appreciable permeability (vs. 5). Comparison of the combined nonvolatile and volatile chemicals with potential for dermal toxicity or with dermal absorption potential according to three models is shown in Fig. 1. There are 56.3% chemicals with potential for dermal toxicity according to FB model and 58% according to ABR model (23.2% only according to PG model).

From among nonvolatile chemicals identified by Abraham and Martins model to have no significant absorption ($Fl^*/Fl > 1$) eight substances: atrazine, o-dichlorobenzene, diuron, metribuzin, napthalene, pentaerythritol, styrene and 1,2,4-trichlorobenzene are identified as substances with potential for dermal absorption by Fiserova-Bergerova et al. but not by Potts and Guy. From among volatile chemicals identified by ABR model to have no significant absorption ($Fl^*/Fl > 1$) four substances: cumene, ethyl benzene, n-hexane and xylene isomers are identified as substances with potential for dermal absorption by Fiserova-Bergerova et al. but not by Potts and Guy. Only one chemical, methylal, is classified as substance with potential for dermal absorption by Abraham and Martins model and not by Fiserova-Bergerova et al. or Potts and Guy. Eight substances: n-butyl acrylate, cyclohexanol, dichloroethyl ether, ethylene glycol, lindane, methoxychlor, methyl isobutyl ketone and nitrotoluene have potential for dermal toxicity according to Abraham and Martins model but there is no significant absorption according to Potts and Guy. All these chemicals have been classified by Fiserova-Bergerova et al.

The simple comparison between the three models can be made by determining the permeability coefficient ratio in pairs. Comparison of the predicted K_p values of the combined dataset of nonvolatile and volatile chemicals according to the models of ABR ($\log K_p$ ABR) and FB ($\log K_p$ FB) and PG ($\log K_p$ PG) is shown in Fig. 2. The regression lines through the data were described. At the selected confidence level (95%), we obtain following results by conventional criteria:

1. For group $\log K_p$ FB (mean −1.293; standard deviation 1.18; size 112) and group Log K_p ABR (mean −1.441; standard deviation 1.04; size 112)–means are not significantly different ($t = 0.9958$).

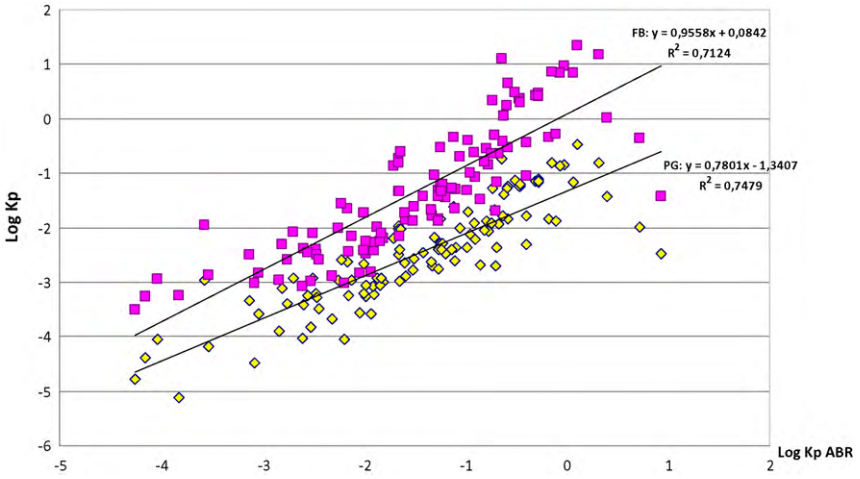

Fig. 2. Comparison of the predicted values of the combined dataset of nonvolatile and volatile chemicals according to the models of Abraham and Martins (2004) ($\log K_p$ ABR) and Fiserova-Bergerova et al. (1990) ($\log K_p$ FB) and Pots and Guy (1993) ($\log K_p$ PG).

2. For group Log K_p PG (mean −2.465; standard deviation 0.943; size 112) and group Log K_p ABR (mean −1.441; standard deviation 1.04; size 112) – means are extremely significantly different (t = 7.7194).

We tried to validate LFER model on the basis of the CLP Regulation. Substances can be allocated in the List of hazardous substances to one of four acute toxicity hazard categories based on acute toxicity by the dermal route according to the numeric criteria expressed as LD_{50} dermal values (between 50 and 2000 mg/kg). From among 94 chemicals which should have the skin notation in the OEL list according LFER model, 81 were placed in the EU hazardous substances list. Thirty three chemicals were classified as fatal, toxic or harmful in contact with skin but 18 compounds were classified as causing skin corrosion or irritation, 11 chemicals were provided with risk phrase indicating that repeated exposure may cause skin dryness or cracking. The remaining 19 chemicals were not classified as hazardous in contact with skin and there was no indication of whether this was due to missing data, inconclusive data, or data which are conclusive although insufficient for the classification. Only xylene isomers did not have skin notation according to LFER model but were classified as hazardous in contact with skin. Xylene also did not have skin notation in ACGIH list of occupational exposure limits.

4. Conclusions

The application LFER model, based on the solvation equation, or linear free-energy relationship which contains five main descriptors predicted from chemical structure: solute excess molar refractivity, dipolarity/polarisability, summation hydrogen bond acidity and basicity, and the McGowan characteristic volume to calculate permeability coefficients and flux values (dermal penetration rate). If the accessibility of experimental data on the dermal uptake is limited we can use this simple model to obtain a rough estimate of the percutaneous absorption.

It is feasible to predict skin notation on the basis of LFER model calculations and Fiserova-Bergerova et al. approach comprising maximum admissible concentrations as the basis to calculate the critical flux.

When using occupational exposure limits as a part of the criteria for skin notation to calculate the critical flux, it is also necessary to remember that some OELs have been established to protect against irritation of mucous membrane but not systemic effects. It is necessary to verify the predicted skin notation for these substances in the future. If we could establish new hygienic standards for some chemicals based on systemic critical effects in addition to OELs based on irritation, it would be possible to use the new values to predict the skin notation again.

Comparison of the calculated permeability coefficient values with data obtained earlier from other models showed that LFER predictions were comparable to Fiserova-Bergerova estimation but differences were extremely significant compared with Potts and Guy alternative model at the selected confidence level (95%); thus, it seems reasonable to conclude that the results of LFER model are consistent with those of Fiserova-Bergerova et al. In Pots and Guy opinion, the paper of Fiserova-Bergerova presents conservative estimates of potential dermal penetration risk. But from our point of view, simple lipid pathway permeation model of PG leads to fewer chemicals being identified as dermal hazard than FB or ABR method. Skin should not be characterised as a simple lipophilic barrier alone. Both lipophilic and polar pathways of permeation exist across the stratum corneum.

From among 112 chemicals, 94 (84%) should have the skin notation in the OEL list and 18 should not based on the LFER calculations. The skin notation had been previously estimated by Fiserova-Bergerova et al. for almost 94% of these chemicals. Twenty-nine (25.8%) chemicals were identified to have significant absorption and 65 (58%) the potential for dermal toxicity. There are 56.25% chemicals with potential for dermal toxicity according to FB model and 23.21% only according to PG model. The optimisation of the ability to accurately predict percutaneous penetration will play a vital role in the assessment of risks associated with exposure to chemicals. It can be useful in the future to apply LFER model using European Union occupational exposure limits to estimate critical flux as reference value.

Conflicts of interest

Nothing declared.

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