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Review

Chemical–biological interactions in human

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Abstract—Chemical–biological interactions in human are currently attracting our attention particularly in the area of QSAR (quantitative structure–activity relationships). In the present review, an attempt has been made to collect the data for the effect of chemicals in human and discussed by the formulation of a total number of 37 QSAR.

Contents

1. Introduction

The most important system for understanding chemical–biological interactions is the human body. Unfortunately, very little work has been done in this area. However, over the last 40 years as we have been deriving and entering equations into our database[1,2] (that now contains 11,950 equations); we have managed to collect some interesting equations on humans. It now seems worthwhile to present our results in an organized way. Naturally it would not be possible, in general, to develop equations for drug development from people. Still, this work shows that it is not completely out of the question. For example, Shulgin tested hundreds of chemicals on themselves and their friends to assay their

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hallucinogenic properties.[3,4] Apparently no ill effects were noticed in these unique studies.

2. Materials and methods

All the data have been collected from the literature (see individual QSAR for respective references). Physicochemical descriptors are auto-loaded, and multiregression analyses (MRA) used to derive the QSAR is executed with the C-QSAR program.[1] The parameters used in this review have already been discussed.[5] Briefly, Clog P is the calculated octanol/water partition coefficient. Mlog P is the experimentally obtained partition coefficient. The Hammett parameters are σ, σ^-, σ^+ and σ_I. The sterimol parameters $B1$, $B5$ and L are calculated values where $B1$ is largely the steric effect of the first atom of a substituent. $B5$ is an attempt to define width of the whole substituent and L defines its length. MgVol is the calculated molar volume of the substituent. NVE (number of valence electrons) is a parameter[6] that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule, for example, H = 1, C = 4, N = 5, O = 6, P = 5, S = 6 and halogens = 7. I is an indicator variable that takes the value of 1 or 0 for structural features that cannot be defined by the normal parameters. In QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction and s is the standard deviation. All the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced.

3. Results and discussion

3.1. Taste

An area that is easy to study and where serious toxicity can be avoided is that of taste. A number of studies have been made on the different acids that occur in beer to better understand how to improve the flavor. Gardner[7] has made an extensive review of this work and shown via QSAR, that the hydrophobicity of the compounds is of central importance in effecting the sour taste of a variety of acids. Many of these studies are based on too few compounds that do not yield very good correlations. The following examples are of interest. The sour taste of these compounds is characterized by $1/T$, where T is the equimolar sour concentration.

Data from Harrison[8] (Table 1)

$$\log 1/T = 0.64(\pm 0.24)\ \text{Clog}P + 2.79(\pm 0.34)$$
$$n = 9,\quad r^2 = 0.849,\quad s = 0.364,\quad q^2 = 0.776 \qquad (1)$$
outliers: butyric acid; phenylacetic acid

Data from Engan[9] (Table 2)

$$\log 1/T = 0.47(\pm 0.10)\ \text{Clog}P + 3.14(\pm 0.25)$$
$$n = 16,\quad r^2 = 0.875,\quad s = 0.410,\quad q^2 = 0.846 \qquad (2)$$
outliers: butyric acid; tartaric acid

Table 1. Sour taste of miscellaneous acids

No.	Compound	log 1/T (Eq. 1)		Clog P
		Obsd	Pred.	
1	Acetic acid	2.48	2.67	−0.19
2	Propanoic acid	2.87	3.00	0.33
3[a]	Butyric acid	4.94	3.34	0.86
4	isobutyric acid	2.64	3.20	0.64
5	Valeric acid	3.46	3.68	1.39
6	isovaleric acid	4.11	3.59	1.26
7	Hexanoic acid	4.37	4.01	1.92
8	Octanoic acid	4.56	4.68	2.98
9	Lactic acid	2.35	2.32	−0.73
10	Pyruvic acid	2.55	2.23	−0.88
11[a]	Phenylacetic acid	5.13	3.68	1.41

[a] Not used in the derivation of Eq. 1.

Table 2. Sour taste of miscellaneous acids

No.	Compound	log 1/T (Eq. 2)		Clog P
		Obsd.	Pred.	
1	Acetic acid	2.48	3.05	−0.19
2	Propanoic acid	2.87	3.30	0.34
3[a]	Butyric acid	4.64	3.54	0.86
4	isobutyric acid	3.25	3.45	0.64
5	Valeric acid	4.31	3.80	1.39
6	isovaleric acid	4.61	3.74	1.26
7	Hexanoic acid	4.37	4.05	1.92
8	Octanoic acid	4.46	4.54	2.98
9	Nonanoic acid	4.50	4.79	3.51
10	Decanoic acid	4.93	5.04	4.04
11	Undecanoic acid	5.27	5.29	4.57
12	Dodecanoic acid	5.60	5.54	5.10
13	Lactic acid	2.35	2.80	−0.73
14	Citric acid	2.74	2.20	−2.00
15[a]	Tartaric acid	2.70	1.63	−3.22
16	Maleic acid	2.58	2.43	−1.52
17	Malonic acid	2.62	2.81	−0.71
18	Succinic acid	2.77	2.90	−0.53

[a] Not used in the derivation of Eq. 2.

Engan extended the study of data set 1 so it is not surprising that the results are very similar.

Data from Meilgaard[10] (Table 3)

$$\log 1/T = 1.04(\pm 0.76)\ \text{CMR} - 2.36(\pm 1.04) \times \log(\beta \times 10^{\text{CMR}} + 1) + 0.74(\pm 0.24)\ \text{Clog}P + 1.49(\pm 1.31)$$
$$n = 18,\quad r^2 = 0.876,\quad s = 0.406,$$
$$q^2 = 0.816\quad \log \beta = -2.66$$
outliers: tartaric acid; phenylacetic acid; fumaric acid
optimum CMR = 2.56
(3)

In the study by Meilgaard, we find a linear relationship between potency and hydrophobicity as in Eqs. 1 and 2, but also a bilinear correlation with CMR, the reason for this is not clear. It could have to do with the time allotted to detect the sour effect. See Ref. 5, p. 195, for a discussion of bilinear model.

Table 3. Sour taste of miscellaneous acids

No.	Compound	log 1/*T* (Eq. 3)		CMR	Clog *P*
		Obsd.	Pred.		
1	Acetic acid	2.54	2.47	1.29	−0.19
2	Propanoic acid	2.69	3.26	1.76	0.34
3	Butyric acid	4.60	3.94	2.22	0.86
4	isobutyric acid	3.47	3.78	2.22	0.65
5	Valeric acid	4.11	4.39	2.69	1.39
6	isovaleric acid	4.83	4.29	2.69	1.26
7	Hexanoic acid	4.16	4.56	3.15	1.92
8	3-Hexenoic acid	4.94	4.37	3.12	1.64
9	Octanoic acid	4.01	4.37	4.08	2.98
10	2-Nonenoic acid	3.96	4.13	4.59	3.52
11	Decanoic acid	4.24	3.97	5.00	4.04
12	Lactic acid	2.35	2.58	1.91	−0.73
13	Pyruvic acid	2.47	2.39	1.79	−0.88
14[a]	Tartaric acid	2.40	−4.66	2.72	−3.22
15[a]	Phenylacetic acid	4.74	−2.66	3.81	1.41
16	Glyoxylic acid	1.57	1.34	1.33	−1.76
17	Oxalactic acid	2.42	2.54	2.45	−1.11
18[a]	Fumaric acid	2.46	−2.16	2.54	−0.17
19	Vanillic acid	3.32	3.12	4.11	1.35
20	Gallic acid	2.67	2.81	3.80	0.43
21	*p*-Coumaric acid	2.50	2.54	4.70	1.57

[a] Not used in the derivation of Eq. 3.

Some studies have been made where the acids were dissolved in oil for testing. Eqs. 4 and 5 show the effect.

Data from Siek et al.[11] (Table 4)

$$\log 1/C = -0.54(\pm 0.11)\ \mathrm{Clog}P + 5.43(\pm 0.65)$$
$$n = 8, \quad r^2 = 0.958, \quad s = 0.355, \quad q^2 = 0.927 \qquad (4)$$
outliers: acetic acid; octanoic acid

Under this condition, it is of interest to note that taste is related to negative hydrophobicity. The compound must get out of the oil to be detected. The observed taste is actually a function of both the compound's intrinsic taste and its ability to partition out of the oil phase. Both of these are governed by hydrophobicity with partitioning out of the oil phase being the more important process governing observed taste.

Hydrophobic compounds tend to remain in the oil phase. It must be remembered that the acids will be largely ionized and that Clog *P* is the calculated value for the un-ionized form of the acids. Since most of the acids are ionized to about the same degree, a reasonable correlation can be obtained. The intercepts for these equations, however, cannot be compared with equations for un-ionized molecules. Eqs. 1–3 are like hundreds of others that we have found for nonspecific effects such as membrane perturbation.

Table 4. Sour taste of miscellaneous acids in oil

No.	Compound	log 1/*T* (Eq. 4)		Clog *P*
		Obsd.	Pred.	
1[a]	Acetic acid	3.93	5.54	−0.19
2	Butyric acid	5.12	4.97	0.86
3	Hexanoic acid	4.67	4.39	1.92
4[a]	Octanoic acid	2.61	3.82	2.98
5	Decanoic acid	2.93	3.25	4.04
6	Dodecanoic acid	2.46	2.67	5.10
7	Tetradecanoic acid	1.66	2.10	6.15
8	Hexadecanoic acid	1.41	1.53	7.21
9	Octadecanoic acid	1.28	0.96	8.27
10	Oleic acid	1.55	1.21	7.79

[a] Not used in the derivation of Eq. 4.

Table 5. Sour taste of miscellaneous acids in oil

No.	Compound	log 1/*T* (Eq. 5)		Clog *P*
		Obsd.	Pred.	
1	Butyric acid	5.17	5.24	0.86
2	Hexanoic acid	4.67	4.52	1.92
3[a]	Octanoic acid	2.61	3.81	2.98
4	Decanoic acid	2.93	3.09	4.04
5	Dodecanoic acid	2.46	2.38	5.10

[a] Not used in the derivation of Eq. 5.

Data from Patton[12] for acids dissolved in oil (Table 5)

$$\log 1/T = -0.68(\pm 0.22)\ \mathrm{Clog}P + 5.82(\pm 0.76)$$
$$n = 4, \quad r^2 = 0.989, \quad s = 0.173, \quad q^2 = 0.959 \qquad (5)$$
outlier: octanoic acid

It is of interest that despite the small number of data points, Eq. 5 agrees well with 4.

The studies of acids dissolved in oil provide insight on the often observed nonlinear relationship found with hydrophobic terms (Ref. 5, p 189). It was decided early on that as chemicals became more hydrophobic, they became more tightly bound in the first hydrophobic phase encountered in a cell or animal. This meant that they were detained from reaching the receptor site during the time of experiment and a nonlinear relationship resulted. So it is with the oil studies of Eqs. 4 and 5 if there were a wider range in Clog *P*, it would be apparent. It should be possible by varying the amount of oil and the hydrophobicity of the chemicals to obtain nonlinear equations in the taste tests.

A different type of result comes from the studies on nitro/cyano anilines in Eqs. 6 and 7.

Relative sweet taste of X-*anilines*; Data from Iwamura[13] (Table 6)

$$\log \mathrm{RBR} = 1.30(\pm 0.21)\ \mathrm{CMR} - 3.34(\pm 0.92)$$
$$n = 18, \quad r^2 = 0.916, \quad s = 0.213, \quad q^2 = 0.890 \qquad (6)$$
outliers: 3-NO_2, 6-OC_4H_9; 3-NO_2, 6-$OCHMe_2$

Relative sweet taste of 3-NO_2, 6-X-anilines; Data from Blanksma and Hoegen[14] (Table 7)

$$\log \mathrm{RBR} = 1.25(\pm 0.30)\ \mathrm{CMR} - 2.84(\pm 1.32)$$
$$n = 9, \quad r^2 = 0.933, \quad s = 0.192, \quad q^2 = 0.888 \qquad (7)$$

The agreement between Eqs. 6 and 7 is very good, despite the fact that the work was done in two different laboratories with different derivatives and different tasters.

Table 6. Sweet taste of X-anilines

No.	*X*	log RBR (Eq. 6)		CMR
		Obsd.	Pred.	
1	3-NO_2, 6-F	1.26	1.46	3.68
2	3-NO_2, 6-Cl	2.31	2.08	4.16
3	3-NO_2, 6-Br	2.71	2.45	4.45
4	3-NO_2, 6-I	2.98	3.14	4.98
5	3-NO_2	1.21	1.44	3.67
6	3-NO_2, 6-Me	2.17	2.05	4.13
7	3-NO_2, 6-C_3H_7	3.02	3.26	5.06
8	3-NO_2, 6-OH	1.96	1.64	3.82
9	3-NO_2, 6-OMe	2.21	2.25	4.29
10	3-NO_2, 6-OC_2H_5	2.87	2.85	4.75
11	3-NO_2, 6-OC_3H_7	3.46	3.46	5.21
12[a]	3-NO_2, 6-OC_4H_9	2.79	4.06	5.68
13[a]	3-NO_2, 6-$OCH(Me)_2$	2.54	3.46	5.21
14	3-NO_2, 6-$OCH{=}CH_2$	3.06	2.82	4.72
15	3-CN	0.94	1.27	3.54
16	3-CN, 3-CN, 6-Cl	2.13	1.91	4.03
17	3-CN, 6-Br	2.46	2.28	4.31
18	3-CN, 6-OMe	1.89	2.07	4.15
19	3-CN, 6-OC_2H_5	2.63	2.68	4.62
20	3-CN, 6-OC_3H_7	3.11	3.28	5.08

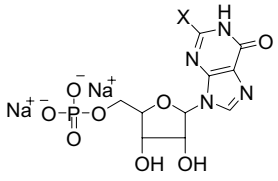
[a] Not used in deriving Eq. 6; RBR=relative biological response.

Table 7. Sweet taste of 3-NO_2-6-X-anilines

No.	*X*	log RBR (Eq. 7)		CMR
		Obsd.	Pred.	
1	H	1.60	1.76	3.67
2	F	1.60	1.78	3.68
3	OMe	2.52	2.53	4.29
4	OC_2H_5	3.15	3.11	4.75
5	OC_6H_5	3.70	3.69	5.21
6	Cl	2.60	2.37	4.16
7	Br	2.90	2.73	4.45
8	I	3.10	3.39	4.98
9	Me	2.52	2.34	4.13

RBR = Relative biological response.

Taste enhancing activity of 2-X-inosine-5′-phosphates **I**; Data from Mizuta et al.[15] (Table 8)



I

$$\log 1/C = 0.82(\pm 0.52)\sigma_{I,x} + 0.16(\pm 0.07)B5_X - 0.22(\pm 0.09)$$
$$n = 12, \quad r^2 = 0.843, \quad s = 0.109, \quad q^2 = 0.757 \qquad (8)$$
$$\textit{outliers}: \ SCH_3; \ OCH(CH_3)_2$$

The sterimol parameter $B5_X$ in Eq. 8 may be replaced by hydrophobic term resulting Eq. 9.

Table 8. Taste enhancing activity of 2-X-inosine-5′-phosphates **I**

No.	*X*	Obsd. $\log 1/C$	Pred. $\log 1/C$		$B5_X$	σ_{IX}	Clog *P*
			Eq. 8	Eq. 9			
1	SC_3H_7	0.93	0.88	0.82	4.98	0.24	−1.92
2	SC_2H_5	0.82	0.73	0.70	3.97	0.25	−2.45
3[a,b]	SCH_3	0.88	0.62	0.56	3.26	0.25	−2.97
4[a]	$OCH(Me)_2$	0.59	0.76	0.71	4.10	0.26	−2.41
5	OC_2H_5	0.68	0.66	0.64	3.36	0.28	−2.72
6	OCH_3	0.49	0.61	0.50	3.07	0.27	−3.25
7[b]	NH_2	0.44	0.32	0.16	1.97	0.12	−4.21
8	NHMe	0.35	0.50	0.37	3.08	0.13	−3.39
9	$N(Me)_2$	0.34	0.44	0.35	3.08	0.06	−3.28
10	CH_3	0.34	0.20	0.19	2.04	−0.04	−3.67
11	C_2H_5	0.34	0.40	0.34	3.17	−0.01	−3.15
12	Cl	0.58	0.58	0.59	1.80	0.47	−3.45
13	C_6H_5	0.55	0.49	0.70	3.11	0.12	−2.08
14	H	0.00	0.07	0.08	1.00	0.00	−4.17

[a] Not used in deriving Eq. 8.
[b] Not used in deriving Eq. 9.

$$\log 1/C = 0.26(\pm 0.11)\ \text{Clog}P + 0.67(\pm 0.51)\sigma_{I,x} + 1.15(\pm 0.38)$$
$$n = 12, \quad r^2 = 0.856, \quad s = 0.105, \quad q^2 = 0.732 \qquad (9)$$
$$\textit{outliers}: \ SCH_3; \ NH_2$$

In Eqs. 8 and 9, we find an electronic term, σ_I, that shows that a decrease in the electron density in the ring to be significant in taste.

3.2. Odor

Pyrazines **II** with bell pepper aroma in water; Data from Buchbauer et al.[16] (Table 9)

II

$$\log 1/C = 1.94(\pm 0.98)\ \text{Clog}P - 0.33(\pm 0.12)\ \text{Clog}P^2 - 3.94(\pm 1.84)\sigma + 2.15(\pm 0.70)B5_2 - 2.68(\pm 0.56)B5_5 - 3.80(0.21)$$
$$n = 33, \quad r^2 = 0.879, \quad s = 0.575, \quad q^2 = 0.813,$$
$$\textit{optimum}\ C\log P = 2.95\ (2.3\text{–}3.3) \qquad (10)$$

See Table 9 for three outliers.

C in Eq. 10 is concentration for the odor threshold. Eq. 10 describes a complex set of ligands and brings out the importance of steric and electronic effects of substituents in the 2- and 5-positions. *B5* is the sterimol parameter that attempts to define the width of substituents (Ref. 5, p 76). It is of interest that 2-substituents have a positive steric effect while 5 have a negative steric effect. This is obviously due to the kind of substituents in these

Table 9. Pyrazines **II** with bell pepper aroma in water

No.	Substituents	Obsd. log 1/*C*	Pred. log 1/*C*		σ	Clog *P*	$B5_2$	$B5_5$
			Eq. 10	Eq. 11				
1[b]	2-Me, 3-$(CH_2)_2CH_3$	1.22	1.42	4.16	−0.30	1.69	2.04	1.00
2	2-OMe, 3-$(CH_2)_2CH_3$	3.92	4.36	4.43	−0.40	2.20	3.07	1.00
3[b]	2-SMe, 3-$(CH_2)_2CH_3$	3.00	3.81	4.51	−0.13	2.45	3.26	1.00
4[b]	2-Me, 3-$CHMe_2$	1.80	1.39	4.07	−0.32	1.56	2.04	1.00
5	2-OMe, 3-$CHMe_2$	4.62	4.08	4.14	−0.42	1.67	3.07	1.00
6	2-OMe, 3-$CHMe_2$, 6-Me	4.35	5.09	4.42	−0.59	2.16	3.07	1.00
7	2-OMe, 3-$CHMe_2$, 5-OMe, 6-Me	1.15	0.79	0.73	−0.86	2.70	3.07	3.07
8	2-OMe, 3-$CHMe_2$, 5-OMe, 6-$CHMe_2$	0.17	0.70	0.72	−0.84	3.23	3.07	3.07
9	2-SMe, 3-$CHMe_2$	4.33	3.38	4.11	−0.15	1.62	3.26	1.00
10	2-OMe, 3-$(CH_2)_3CH_3$	4.30	4.64	4.56	−0.43	2.72	3.07	1.00
11[b]	2-Me, 3-CH_2CHMe_2	0.89	1.66	4.39	−0.29	2.09	2.04	1.00
12	2-OMe, 3-CH_2CHMe_2	5.25	4.46	4.54	−0.39	2.59	3.07	1.00
13[a]	2-OMe, 3-CH_2CHMe_2, 6-Me	3.59	5.17	4.56	−0.56	3.09	3.07	1.00
14	2-OMe, 3-CH_2CHMe_2, 5-Me	2.59	2.38	2.64	−0.56	3.09	3.07	2.04
15	2-SMe, 3-CH_2CHMe_2	3.48	3.84	4.57	−0.12	2.85	3.26	1.00
16	2-OMe, 3-$CH(Me)CH_2CH_3$	4.40	4.32	4.43	−0.39	2.19	3.07	1.00
17	2-OMe, 3-$(CH_2)_4CH_3$	4.70	4.59	4.53	−0.42	3.25	3.07	1.00
18	2-OCH_2CH_3, 3-$(CH_2)_4CH_3$	4.10	4.89	4.35	−0.39	3.78	3.36	1.00
19	2-SMe, 3-$(CH_2)_4CH_3$	3.92	3.86	4.47	−0.15	3.51	3.26	1.00
20[a,b]	2-SCH_2CH_3, 3-$(CH_2)_4CH_3$	3.00	4.98	4.21	−0.12	4.03	3.97	1.00
21	2-OMe, 3-$(CH_2)_2CHMe_2$	5.20	4.93	4.56	−0.50	3.12	3.07	1.00
22	2-OMe, 3-$CH_2CH(Me)CH_2CH_3$(E)	4.92	4.65	4.56	−0.43	3.12	3.07	1.00
23	2-OMe, 3-$(CH_2)_3CH{=}CH_2$	4.52	4.65	4.56	−0.43	2.77	3.07	1.00
24	2-OMe, 3-$(CH_2)_2CH{=}CHMe$(E)	3.89	4.65	4.56	−0.43	2.77	3.07	1.00
25[a,b]	2-OMe, 3-$(CH_2)_2CH{=}CHMe$(Z)	3.30	4.65	4.56	−0.43	2.77	3.07	1.00
26	2-OMe, 3-$(CH_2)_5CH_3$	4.15	4.43	4.35	−0.43	3.78	3.07	1.00
27	2-OMe, 3-$(CH_2)_3CHMe_2$	5.22	4.50	4.41	−0.43	3.65	3.07	1.00
28	2-OMe, 3-$CH_2CH(Me)(CH_2)_2CH_3$	5.10	4.95	4.41	−0.43	3.65	3.07	1.00
29	2-OMe, 3-$(CH_2)_6CH_3$	4.59	4.05	4.02	−0.43	4.31	3.07	1.00
30	2-OMe, 3-$(CH_2)_7CH_3$	4.22	3.48	3.53	−0.43	4.84	3.07	1.00
31	2-OCH_2CH_3, 3-$(CH_2)_7CH_3$	2.70	3.23	2.88	−0.40	5.37	3.36	1.00
32	2-SMe, 3-$(CH_2)_7CH_3$	3.15	2.49	3.24	−0.16	5.09	3.26	1.00
33	2-SCH_2CH_3, 3-$(CH_2)_7CH_3$	2.70	3.05	2.51	−0.13	5.62	3.97	1.00
34	2-OMe, 3-$(CH_2)_9CH_3$	1.40	1.79	2.08	−0.43	5.90	3.07	1.00
35	2-OCH_2CH_3, 3-$(CH_2)_9CH_3$	1.22	1.17	1.12	−0.40	6.43	3.36	1.00
36	2-OMe, 3-Me, 5-OMe, 6-Me	0.74	0.69	0.59	−0.88	2.17	3.07	3.07

[a] Not used in the derivation of Eq. 10.
[b] Not used in the derivation of Eq. 11.

positions, since the parent molecule is symmetrical. The same applies to the lack of steric effects in the 3 and 6 positions. Another aspect of the steric effect is that the *cis* form of $CH_2CH_2CH{=}CHCH_3$ is a very bad fit, while the *trans* form is a much better fit.

Eq. 10 may be modified as Eq. 11 by considering only two parameters.

$$\log 1/C = 1.62(\pm 0.97)\ \mathrm{Clog}P - 0.28(\pm 0.12)\ \mathrm{Clog}P^2 - 1.85(\pm 0.33)B5_5 + 4.07(\pm 1.84)$$
$$n = 30, \quad r^2 = 0.870, \quad s = 0.542, \quad q^2 = 0.834,$$
$$\textit{optimum}\ C\log P = 2.90\ (2.01\text{–}3.31) \tag{11}$$

See Table 9 for six outliers.

Pyrazines occur in a variety of foods in addition to bell peppers, for example, bread, meats, potatoes, coffee. Thus, it is important to understand this via QSAR. Clearly, hydrophobicity is highly important, as are electron-releasing substituents (negative σ term). This would increase basicity of the compounds.

Nasal pungency of miscellaneous chemicals; Data from Hau et al.[17] (Table 10)

$$\log \mathrm{NPT} = -0.70(\pm 0.12)\ \mathrm{Clog}P - 1.62(\pm 0.53)I + 4.46(\pm 0.27)$$
$$n = 31, \quad r^2 = 0.853, \quad s = 0.464, \quad q^2 = 0.829$$
$$\textit{outliers}: \ C_5H_5N;\ CH{\equiv}C(CH_2)_5CH_3$$
$$I = 1 \text{ for phenyl derivatives} \tag{12a}$$

If the alcohols are run as a group, Eq. 12b is obtained.

$$\log \mathrm{NPT} = -0.68(\pm 0.16)\ \mathrm{Clog}P + 4.00(\pm 0.23)$$
$$n = 10, \quad r^2 = 0.925, \quad s = 0.246, \quad q^2 = 0\ .898$$
$$\textit{outlier}: \ \textit{tert}\text{-butanol} \tag{12b}$$

Table 10. Nasal pungency of miscellaneous chemicals

No.	Compound	log NPT (Eq. 12a)		Clog *P*	*I*
		Obsd.	Pred.		
1	MeOH	4.53	4.99	−0.76	0
2	C_2H_5OH	3.91	4.62	−0.24	0
3	C_3H_7OH	3.49	4.25	0.29	0
4	$CHMe_2OH$	4.26	4.41	0.07	0
5	C_4H_9OH	3.20	3.88	0.82	0
6	s-C_4H_9OH	3.98	4.04	0.60	0
7	CMe_3OH	4.52	4.12	0.47	0
8	$C_5H_{11}OH$	3.21	3.51	1.35	0
9	$C_6H_{13}OH$	2.62	3.14	1.88	0
10	$C_7H_{15}OH$	2.32	2.77	2.41	0
11	$C_8H_{17}OH$	1.99	2.40	2.94	0
12	MeOAc	5.05	4.33	0.18	0
13	C_2H_5OAc	4.83	3.96	0.71	0
14	C_3H_7OAc	4.25	3.59	1.24	0
15	C_4H_9OAc	3.56	3.22	1.77	0
16	s-C_4H_9OAc	3.60	3.38	1.55	0
17	CMe_3OAc	3.98	3.47	1.42	0
18	$C_5H_{11}OAc$	3.22	2.85	2.30	0
19	$C_6H_{13}OAc$	2.80	2.48	2.83	0
20	$C_7H_{15}OAc$	2.49	2.11	3.36	0
21	$C_8H_{17}OAc$	1.95	1.74	3.89	0
22	$C_{10}H_{21}OAc$	0.70	1.00	4.94	0
23	$C_{12}H_{25}OAc$	0.10	0.26	6.00	0
24	$MeCOMe_2$	5.12	4.61	−0.21	0
25	C_3H_7COMe	3.47	3.87	0.85	0
26	$C_5H_{11}COMe$	2.91	3.13	1.91	0
27	$C_7H_{15}COMe$	2.53	2.39	2.97	0
28[a]	C_5H_5N	3.11	4.01	0.65	0
29	C_6H_5Me	4.47	4.23	2.64	1
30	$C_6H_5C_2H_5$	4.00	3.86	3.17	1
31	$C_6H_5C_3H_7$	3.17	3.49	3.70	1
32	C_6H_5Cl	4.02	4.08	2.86	1
33[a]	$CH{\equiv}C(CH_2)_5CH_3$	4.49	1.97	3.57	0

[a] Not used in the derivation of Eq. 12a.

Running the esters alone yields Eq. 12c.

$$\log \mathrm{NPT} = -0.87(\pm 0.06)\ \mathrm{Clog}P + 5.23(\pm 0.19)$$
$$n = 12, \quad r^2 = 0.990, \quad s = 0.161, \quad q^2 = 0.985 \tag{12c}$$

Olfactory detection threshold of alcohols; Data from Wolkowski et al.[18] (Table 11)

$$\log 1/C = 2.33(\pm 0.68)\ \mathrm{Clog}P - 2.58(\pm 1.0) \times \log(\beta \times 10^{\mathrm{Clog}P} + 1) + 6.48(\pm 0.50)$$
$$n = 12, \quad r^2 = 0.919, \quad s = 0.537, \quad q^2 = 0.859, \tag{13}$$
optimum $\mathrm{Clog}P = 2.4, \log \beta = -1.40$
outlier: allyl alcohol

Olfactory detection threshold of hydrocarbons; Data from Wolkowski et al.[18] (Table 12)

$$\log 1/C = 0.84(\pm 0.26)\ \mathrm{Clog}P + 2.78(\pm 1.1)$$
$$n = 11, \quad r^2 = 0.857, \quad s = 0.546, \quad q^2 = 0.777 \tag{14}$$
outliers: dodecane; cyclohexane

It is interesting that the equation for hydrocarbons is linear while that for the alcohols shows an optimum at

Table 11. Olfactory detection threshold of alcohols

No.	Compound	log 1/*C* (Eq. 13)		Clog *P*
		Obsd.	Pred.	
1	Methanol	5.08	4.69	−0.76
2	Ethanol	5.59	5.90	−0.24
3	Propanol	7.18	7.07	0.29
4	*s*-Propanol	6.51	6.60	0.07
5	Butanol	8.24	8.13	0.82
6	*tert*-Butanol	6.74	7.45	0.47
7	Pentanol	9.66	8.90	1.35
8	Hexanol	9.77	9.29	1.88
9	Heptanol	8.54	9.37	2.41
10	Octanol	9.30	9.31	2.94
11	Decanol	9.01	9.07	4.00
12	Dodecanol	8.96	8.81	5.06
13[a]	Allyl alcohol	8.05	6.47	0.01

[a] Not used in the derivation of Eq. 13.

Table 12. Olfactor detection threshold of hydrocarbons

No.	Compound	log 1/*C* (Eq. 14)		Clog *P*
		Obsd.	Pred.	
1	Ethane	3.71	4.28	1.75
2	Propane	4.15	4.69	2.28
3	Butane	5.61	5.13	2.81
4	Pentane	6.32	5.57	3.34
5	2,4-Dimethylpentane	5.54	6.24	4.14
6	Hexane	6.41	6.01	3.87
7	Heptane	6.87	6.50	4.40
8	Octane	7.22	6.90	4.93
9	Nonane	7.17	7.34	5.45
10	Decane	7.94	7.78	5.98
11[a]	Dodecane	7.50	8.66	7.04
12	Undecane	7.64	8.22	6.51
13[a]	Cyclohexane	6.50	5.58	3.35

[a] Not used in the derivation of Eq. 14.

2.4. This value is close to optimum found for chemical perfusions in the animal body.[19] Hydrocarbons appear to move about more freely than alcohols.

3.3. Dealkylation

Demethylation of X-$C_6H_4N(Me)_2$ by Cytochrome P-450; Hansch[20] (Table 13)

$$\log 1/k_m = 0.63(\pm 0.30)\sigma^- + 0.46(\pm 0.35)\log P + 2.62(\pm 0.99)$$
$$n = 8, \quad r^2 = 0.861, \quad s = 0.137, \quad q^2 = 0.684 \tag{15}$$
outlier: 4-CHO

$$\log k_{cat} = -0.68(\pm 0.12)\sigma^- + 1.06(\pm 0.07)$$
$$n = 8, \quad r^2 = 0.971, \quad s = 0.065, \quad q^2 = 0.936 \tag{16}$$
outlier: 4-CHO

$$\log k_{cat}/k_m = 0.53(\pm 0.19)\log P + 3.47(\pm 0.53)$$
$$n = 8, \quad r^2 = 0.879, \quad s = 0.093, \quad q^2 = 0.823 \tag{17}$$
outlier: 4-CHO

Table 13. Dealkylation of X-$C_6H_4N(Me)_2$ by cytochrome P-450

No.	X	$\log 1/k_m$ (Eq. 15)		$\log 1/k_{cat}$ (Eq. 16)		$\log k_{cat}/k_m$ (Eq. 17)		$\log P$	σ^-
		Obsd.	Pred.	Obsd.	Pred.	Obsd.	Pred.		
1	3-Me	3.82	3.86	1.17	1.10	4.99	4.95	2.80	−0.07
2	4-Me	3.80	3.80	1.10	1.16	4.90	4.69	2.81	−0.15
3	H	3.59	3.68	1.03	1.06	4.62	4.69	2.31	0.00
4	4-F	4.10	3.87	0.96	1.02	5.06	4.87	2.65	0.05
5	4-Cl	4.15	4.27	0.95	0.87	5.10	5.17	3.22	0.27
6	4-Br	4.38	4.34	0.88	0.87	5.25	5.25	3.37	0.28
7[a]	4-CHO	3.43	4.09	0.63	0.36	4.06	4.43	1.81	1.03
8	4-CN	4.15	4.24	0.43	0.38	4.58	4.62	2.17	1.00
9	4-NO_2	4.52	4.44	0.15	0.21	4.67	4.67	2.27	1.24

[a] Not used in the derivation of Eqs. 15–17.

Looking at the individual sets, we see a role for σ^- in Eqs. 15 and 16 of equal magnitude but of opposite sign so that they cancel in Eq. 17. This is very interesting information as such a result may well occur in many equations where only the overall reaction of Eq. 17 is observed in the form of the Michaelis–Menten equation (Ref. 5, p 232). The data for Eqs. 15–17 comes from the exceptional work in Guengerich's laboratory.[21] This series of equations explain why we can avoid doing such a study and simply base equations on a single study (e.g., $\log 1/C$).

We can now compare the above equations with the microsomal demethylation of the amines in Table 14[20] from which Eq. 18 was formulated.

$$\log k_m = 0.68(\pm 0.13)\log P + 2.91(\pm 0.28)$$
$$n = 12, \quad r^2 = 0.928, \quad s = 0.243, \quad q^2 = 0.897 \qquad (18)$$
outliers: codeine; ephedrine

As can be seen from Table 14, a rather mixed group of amines are covered by Eq. 18. It is not possible to use Hammett constants to search for an electronic effect.

Table 14. Rate of microsomal demethylation of amines

No.	Compound	$\log k_m$ (Eq. 18)		$\log P$
		Obsd.	Pred.	
1	2-Dimethylaminonaphthalene	5.63	5.33	3.55
2	3-Cl-*N*,*N*-dimethylamino-benzene	4.94	5.16	3.29
3	3-Me-*N*,*N*-dimethylamino-benzene	4.73	4.83	2.81
4	4-Me-*N*,*N*-dimethylamino-benzene	4.70	4.83	2.80
5	Dimethylaminobenzene	4.19	4.49	2.32
6	4-Amino-*N*,*N*-dimethylamino-benzene	3.87	3.65	1.08
7	Caffeine	2.86	2.86	−0.07
8	3-Amino-*N*,*N*-dimethylamino-benzene	3.85	3.65	1.08
9	Pentobarbital	4.48	4.30	2.03
10	Hexobarbital	4.22	3.93	1.50
11[a]	Codeine	3.36	3.77	1.26
12[a]	Ephedrine	1.97	3.55	0.93
13	Barbital	3.00	3.35	0.65
14	Physostigmine	2.94	3.03	0.17

[a] Not used to derive Eq. 18. k_m is the rate of oxidation that is determined by the binding alone.

Table 15. Dealkylation of $C_6H_5CH_2CH(Me)N(R_1)R_2$ by human

No.	R_1	R_2	$\log k$ (Eq. 19)		$\log P$
			Obsd.	Pred.	
1	Me	H	−1.84	−2.01	1.74
2	C_2H_5	H	−1.69	−1.68	2.27
3	C_3H_7	H	−1.51	−1.36	2.80
4	$CH(Me)_2$	H	−1.66	−1.50	2.58
5	C_4H_9	H	−1.53	−1.04	3.33
6[a]	$CH(Me)C_2H_5$	H	−1.71	−1.17	3.11
7[a]	$CH_2C_6H_5$	H	−1.49	−0.77	3.77
8	Me	Me	−1.57	−1.81	2.06
9	C_2H_5	C_2H_3	−1.26	−1.26	2.96
10	C_3H_7	C_3H_7	−0.73	−0.62	4.02
11	C_4H_9	C_4H_9	0.30	0.28	5.08
12	Me	C_2H_5	−1.52	−1.54	2.51
13	Me	C_3H_7	−1.16	−1.26	2.96
14	Me	C_4H_9	−0.82	−0.94	3.50

[a] Not used to derive Eq. 19.

Nevertheless, the statistics for the equations are good bringing out the fact that steric factors are not significant in the dealkylation step. K_m is the rate of oxidation for the initial binding step.

Dealkylation of $C_6H_5CH_2CH(Me)N(R_1)R_2$ by a human (Table 15)[20]

$$\log k = 0.61(\pm 0.16)\log P - 3.07(\pm 0.51)$$
$$n = 12, \quad r^2 = 0.874, \quad s = 0.221, \quad q^2 = 0.762 \qquad (19)$$
outliers: $R_1 = CH(Me)C_2H_5$, $R_2 = H$; $R_1 = CH_2C_6H_5$, $R_2 = H$

Again, we find steric factors to be of negligible importance. Presumably Cytochrome P-450 is operating to generate the data for Eqs. 15 and 16 as well as 17. Studies such as those covered by Eqs. 15–17 are indeed rare and highly valuable. Eqs. 18 and 19 are to be expected from the results of Eq. 17.

3.4. Miscellaneous antihypertensive drugs acting as β-adrenoreceptor antagonists

Fraction of drug bound to albumin after IV Injection; Data from Hinderling et al.[22] (Table 16)

$$\log k = 0.37(\pm 0.17)\ \mathrm{Clog}P - 1.34(\pm 0.37)$$
$$n = 5, \quad r^2 = 0.938, \quad s = 0.066, \quad q^2 = 0.800 \qquad (20)$$
outlier: timolol

Table 16. Fraction of miscellaneous antihypertensive drugs bound to albumin after IV injection (Eq. 20)

No.	Compound	log$k$ (Eq. 20)		log$k$ (Eq. 21)		log$k$ (Eq. 22)		log$k$ (Eq. 23)		log$k$ (Eq. 24)		Clog$P$
		Obsd.	Pred.	Obsd.	Pred.	Obsd.	Pred.	Obsd.	Pred.	Obsd.	Pred.	
1	Bufuralol	—	—	2.73	2.72	0.60	0.93	−1.70	−1.80	−0.04	0.03	3.40
2	Tolamolol	—	—	2.86	2.75	1.57	1.47	−1.30	−1.09	−0.04	−0.18	2.10
3	Propranolol	−0.26	−0.33	2.83	2.75	1.43	1.20	−1.40	−1.44	−0.03	−0.01	2.75
4	Alprenolol	−0.40	−0.37	2.64	2.75	1.26	1.24	−1.70	−1.39	−0.12	−0.03	2.65
5[b]	Oxprenolol	−0.64	−0.57	2.24	1.17	1.34	1.47	−0.96	−1.09	−0.04	−0.18	2.09
6[c]	Acebutolol	—	—	2.68	2.71	2.47	1.63	−0.39	−0.88	−0.59	−0.33	1.71
7[a]	Timolol	−1.16	−0.76	2.72	2.69	1.85	1.69	−0.92	−0.81	−0.22	−0.39	1.58
8[e]	Metoprolol	−0.80	−0.84	2.85	2.61	1.97	1.79	−0.82	−0.69	−1.10	−0.51	1.35
9[c,d]	Pindolol	−0.75	−0.73	2.43	2.71	2.44	1.65	−0.30	−0.86	−0.23	−0.35	1.67
10	Atenolol	—	—	1.00	0.98	2.23	2.39	−0.03	0.10	−1.52	−1.62	−0.11
11[e]	Nadolol	—	—	1.69	1.75	2.19	2.19	−0.12	−0.16	−0.55	−1.18	0.38
12	Sotalol	—	—	—	—	2.20	2.25	0.00	−0.08	—	—	0.23
13	Penbutolol	—	—	—	—	—	—	—	—	−0.01	−0.04	4.04
14	Practolol	—	—	—	—	—	—	—	—	−1.16	−0.89	0.76

Non-renal clearance after IV injection of the drugs (Eq. 21); Renal clearance of the drugs after IV injection (Eq. 22); Fraction of the drugs renally excreted unchanged after IV injection (Eq. 23); Fraction of the drugs bound to plasma protein after IV injection (Eq. 24).
[a–e]Not used in the derivation of Eqs. 20–24, respectively.

Non-renal clearance after IV injection; Data from Hinderling et al.[22] (Table 16)

$$\log k = 1.94(\pm 0.61)\ \mathrm{Clog}P - 1.20(\pm 0.80) \times \log(\beta \times 10^{\mathrm{Clog}P} + 1) + 1.29(\pm 0.30)$$
$$n = 10, \quad r^2 = 0.950, \quad s = 0.168, \quad q^2 = 0.918 \qquad (21)$$
outlier: oxprenolol $\log \beta = -0.81$
optimum $\mathrm{Clog}P = 2.35$

Renal clearance of miscellaneous antihypertensive drugs after IV injection; Data from Hinderling et al.[22] (Table 16)

$$\log k = -0.42(\pm 0.12)\ \mathrm{Clog}\ P + 2.35(\pm 0.24)$$
$$n = 10, \quad r^2 = 0.888, \quad s = 0.185, \quad q^2 = 0.793 \qquad (22)$$
outliers: acebutolol; pindolol

Fraction of dose of renally excreted drug unchanged after IV injection; Data from Hinderling et al.[22] (Table 16)

$$\log k = -0.54(\pm 0.15)\ \mathrm{Clog}P + 0.04(\pm 0.29)$$
$$n = 11, \quad r^2 = 0.886, \quad s = 0.228, \quad q^2 = 0.848 \qquad (23)$$
outlier: pindolol

Fraction of drug bound to plasma protein after IV injection; Data from Hinderling et al.[22] (Table 16)

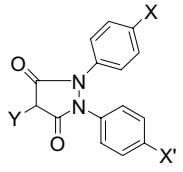
$$\log k = 0.94(\pm 0.32)\ \mathrm{Clog}P - 0.14(\pm 0.08)\ \mathrm{Clog}P^2 - 1.52(\pm 0.33)$$
$$n = 11, \quad r^2 = 0.910, \quad s = 0.173, \quad q^2 = 0.770$$
outliers: metoprolol; nadolol
optimum $\mathrm{Clog}P = 3.31$ (2.8–5.0)
(24)

As far as we know this is the most extensive published analysis of drug interaction in humans from a variety of viewpoints. No doubt other such examples exist in drug company records. Of special interest are Eqs. 21 and 24, where nonlinear QSAR establish optimum hydrophobicity for non-renal clearance and serum protein binding. The confidence limits on the optimal Clog$P$ are not very tight, but the equations do show a relationship between serum protein binding and non-renal clearance that one might expect.

Eqs. 22 and 23 are of great interest in that the negative term indicates that hydrophilic drugs are more important for the renal clearance. Hence our argument for making drugs as hydrophilic as possible commensurate with efficacy.[19]

3.5. Metabolism of phenylbutazones

Metabolism of phenylbutazones**III**; Data from Burnes et al.[23] (Table 17) Half life in hours



III

$$\log T_{1/2} = 0.46(\pm 0.25)\ \mathrm{Clog}P + 0.26(\pm 0.56)$$
$$n = 6, \quad r^2 = 0.865, \quad s = 0.322, \quad q^2 = 0.700 \qquad (25)$$
outlier: $\mathrm{X} = \mathrm{X}' = \mathrm{Me}, \ \mathrm{Y} = \mathrm{C_4H_9}$

The anti-rheumatic drug member of this family is no longer in use as it caused retention of sodium. The interesting aspect of Eq. 25 is that the more hydrophobic compounds have a longer half life, which is probably due to serum binding.

3.6. Cytochrome P-450

Fraction of miscellaneous drugs that are substrates of cytochrome P-450, free in plasma; Data from Davis et al.[24] (Table 18)

Table 17. Metabolism of phenyl butazones **III**

No.	X	X′	Y	log $T_{1/2}$ (Eq. 25)		Clog P
				Obsd.	Pred.	
1	H	H	C_4H_9	1.86	1.81	3.39
2	OH	H	C_4H_9	1.86	1.50	2.72
3[a]	Me	Me	C_4H_9	1.38	2.26	4.38
4	NO_2	H	C_4H_9	1.30	1.69	3.13
5	H	H	$CH_2CH_2CH(OH)CH_3$	0.90	0.80	1.18
6	H	H	$CH_2CH_2SOCH_3$	0.30	0.13	−0.27
7	SO_2Me	SO_2Me	C_4H_9	0.00	0.30	0.10

[a] Not used in the derivation of Eq. 25.

Table 18. Fraction of miscellaneous drugs free in plasma

No.	Compound	log 1/C (Eq. 26)		log P'
		Obsd.	Pred.	
1	Amoidarone	3.70	3.40	6.20
2	Felodipine	2.40	2.57	4.80
3	Nifedipine	1.38	1.42	2.87
4	Haloperidol	1.06	1.33	2.71
5	Bupivacaine	1.28	1.23	2.54
6	Imipramine	0.96	1.22	2.52
7	Triazolam	0.96	0.69	1.63
8	Diltiazem	0.55	0.94	2.05
9	Alfentanil	1.07	0.97	2.11
10	Quinine	1.16	0.97	2.11
11[a]	Amlodipine	1.13	0.34	1.05
12	Lidocaine	0.38	0.65	1.56
13	Dofetilide	0.34	0.29	0.96
14	Erythromycin	0.72	0.29	0.96
15[a]	Disopyramide	0.57	−0.49	−0.36

P' is octanol/water partition coefficient measured at pH 7.4.
[a] Not used in derivation of Eq. 26.

$$\log 1/C = 0.59(\pm 0.12)\log P' - 0.35(\pm 0.28)$$
$$n = 13, \quad r^2 = 0.921, \quad s = 0.267, \quad q^2 = 0.853 \quad (26)$$
outliers: amlodipine; disopyramide

P' is the octanol/water partition coefficient measured at pH 7.4.

3.7. Miscellaneous drugs in breast milk

Miscellaneous drugs in breast milk; Data from Meskin and Lein[25] (Table 19)

$$\log M/P = -0.28(\pm 0.08)\log P' + 0.16(\pm 0.11)\ \text{MgVol} - 1.37(\pm 0.32)I - 0.23(\pm 0.21)$$
$$n = 27, \quad r^2 = 0.826, \quad s = 0.241, \quad q^2 = 0.752$$
$I = 1$ for the presence of –COOH
outliers: aspirin; methotrexate; nalidixic acid; phentoin; thiouracil; tetracycline
(27a)

M/P is the milk/plasma ratio. P' is the measured octanol/water partition coefficient at pH 7.4. Considering the diversity of structures, it is not surprising that there are a number of outliers, most of which are acids. Also one might expect a negative log P' term and of course carboxyl groups have a negative effect. Only a very few drugs have a positive log M/P value.

Table 19. Miscellaneous drugs found in breast milk

No.	Compound	log M/P (Eq. 27a)		log P'	I	MgVol
		Obsd.	Pred.			
1	Acetaminophen	−0.03	−0.17	0.51	0	1.17
2[a]	Aspirin	−0.10	−1.06	−1.15	1	1.29
3	Chloral	−0.59	−0.35	0.99	0	0.88
4	Flufenamic acid	−1.89	−1.88	2.08	1	2.38
5[a]	Methotrexate	−1.00	−0.36	−2.52	1	3.22
6	Metroxidazole	0.00	−0.02	−0.02	0	1.19
7[a]	Nalidixic acid	−0.98	−1.48	0.59	1	1.70
8	Penicillin G	−0.94	−0.69	−1.81	1	1.83
9	Phenactin	−0.23	−0.43	1.59	0	1.45
10	Phenobarbital	−0.65	−0.36	1.47	0	1.70
11	Phenylbutazone	−0.92	−0.72	3.16	0	2.43
12[a]	Phentoin	0.08	−0.61	2.47	0	1.87
13	Salicylic acid	−0.92	−1.17	−0.90	1	0.99
14	Sulfanilamide	0.00	0.15	−0.62	0	1.20
15	Sulfapyridine	−0.10	0.07	0.00	0	1.76
16	Theophylline	−0.17	−0.01	−0.02	0	1.22
17[a]	Thiouracil	0.48	−0.42	1.23	0	0.86
18	Tolbutamide	−0.60	−0.60	2.52	0	2.06
19	Antipyrine	0.00	−0.08	0.38	0	1.49
20	Chlorpromazine	−0.40	−0.74	3.22	0	2.41
21	Codeine	0.34	0.04	0.36	0	2.21
22	Diazepam	−1.00	−0.68	2.80	0	2.07
23	Erythromycin	0.44	0.52	0.66	0	5.77
24	Imipramine	−0.54	−0.54	2.52	0	2.40
25	Isoniazide	0.00	0.15	−0.70	0	1.03
26	Meperidine	0.06	−0.21	1.15	0	2.05
27	Methadone	−0.08	−0.37	2.07	0	2.71
28	Morphine	0.40	0.07	0.15	0	2.07
29	Pseudoephedrine	0.51	0.44	−1.48	0	1.44
30	Pyrimethamine	−0.50	−0.37	1.61	0	1.85
31	Quinine	−0.85	−0.41	2.14	0	2.55
32[a]	Tetracycline	−0.10	0.67	−1.37	0	3.10
33	Triprodlidine	−0.10	−0.36	1.86	0	2.36

M/P=Milk plasma ratio.
[a] Not used in derivation of Eq. 27a.

MgVol is the molar volume for the whole molecule and calculated by C-QSAR program[1] using the method of McGowan.[26] The use of MgVol as a parameter in QSAR has already been discussed.[26–28] The contribution of MgVol in the correlation of Eq. 27a can be seen by comparing Eq. 27a with that of 27b, which was derived with the same outliers.

$$\log M/P = -0.25(\pm 0.09)\log P' - 1.37(\pm 0.37)I + 0.67(\pm 0.15)$$
$$n = 27, \quad r^2 = 0.757, \quad s = 0.279, \quad q^2 = 0.714$$
$$I = 1 \text{ for the presence of –COOH} \tag{27b}$$

Miscellaneous environmental chemicals and their transfer to breast milk; Data from Travis et al.[29] (Table 20)

$$\log \mathrm{BF} = 18.6(\pm 8.5)\ \mathrm{Mlog}\ P - 1.49(\pm 0.70)\ \mathrm{Mlog}\ P^2 - 55(\pm 0.25)$$
$$n = 5, \quad r^2 = 0.990, \quad s = 0.084, \quad q^2 = 0.915$$
$$\textit{optimum}\ \mathrm{Mlog}P = 6.3\ (6.2\text{–}6.5)$$
$$\textit{outlier}\text{: hexachlorobenzene} \tag{28}$$

The data for Eq. 28 was collected from different sources, nevertheless, the optimum $\log P$ is well defined. The much more lipophilic, neutral compounds that Eq. 28 is based on, brings out the environmental danger of these substances. Mlog P = measured $\log P$.

3.8. Absorption of various chemicals to various parts of the human system

Bioconcentration in adipose tissue; Data from Travis et al.[29] (Table 21)

Table 20. Miscellaneous environmental chemicals found in breast milk

No.	Compound	log BF (Eq. 28)		Mlog P
		Obsd.	Pred.	
1	DDE	2.57	2.62	6.96
2	DDT	2.79	2.72	6.91
3	Dieldrin	1.63	1.67	5.20
4	Heptachlor-epoxide	2.30	2.24	5.40
5[a]	Hexachlorobenzene	2.30	2.93	5.73
6	Polychlorobiphenyls	3.22	3.26	6.50

[a] Not used in the derivation of Eq. 28.

Table 21. Bioconcentration of various chemicals in adipose tissue

No.	Compound	log BF (Eq. 29)		Mlog P
		Obsd.	Pred.	
1	Benzene	−1.70	−1.65	2.13
2	DDE	2.86	2.88	6.96
3	DDT	2.44	2.83	6.91
4	Dichloromethane	−1.84	−2.47	1.25
5	Dieldrin	1.27	1.23	5.20
6	Heptachlor-epoxide	2.00	1.42	5.40
7	Hexachlorobenzene	1.91	1.73	5.73
8	1,1,1-Trichloroethane	−1.29	−1.31	2.49
9	Pentachlorophenol	0.82	1.16	5.12
10	Perchloroethylene	−0.76	−0.46	3.40
11	Polychlorinated-biphenyls	2.80	2.45	6.50
12	Trichloroethylene	−1.90	−1.20	2.61

Table 22. Percentage absorbed from oral administration

No.	Compound	log C (Eq. 30)		Clog P
		Obsd.	Pred.	
1	Acarbose	0.18	0.18	−6.68
2	Bisoprolol	2.00	2.00	2.12
3	Cimetidine	2.00	1.89	0.35
4	Fluvastatin	1.99	1.96	4.05
5	Granisetron	1.99	1.99	1.86
6	Isoxepac	1.99	2.00	2.57
7[a]	Lovastatin	1.49	1.94	4.30
8	Nitrendipine	1.94	1.96	4.02
9	Omeprazole	1.99	2.00	2.57
10	Prenalterol	1.99	1.95	1.09
11[a]	Ramipril	1.78	1.99	1.76
12	Sumatriptan	1.79	1.93	0.74

[a] Not used in the derivation of Eq. 30.

$$\log \mathrm{BF} = 0.94(\pm 0.14)\ \mathrm{Mlog}P - 3.64(\pm 0.68)$$
$$n = 12, \quad r^2 = 0.957, \quad s = 0.419, \quad q^2 = 0.933$$
$$\mathrm{BF} = \frac{\text{conc. in adipose tissue}}{\text{average daily intake}} \tag{29}$$

The correlation of the equation is very good considering that BF values came from various laboratories. Optimum $\log P$ is above 6.9 and compares with high values found for Eq. 28.

% Absorption of drugs through oral administration; Data from Chiou et al.[30] (Table 22)

$$\log C = 0.11(\pm 0.02)\ \mathrm{Clog}P - 0.02(\pm 0.00)\ \mathrm{Clog}P^2 + 1.86(\pm 0.09)$$
$$n = 10, \quad r^2 = 0.989, \quad s = 0.068, \quad q^2 = 0.774$$
$$\textit{outliers}\text{: lovastatin; ramipril}$$
$$\textit{optimum}\ \mathrm{Clog}P = 2.62\ (1.73\text{–}4.07) \tag{30}$$

Table 23. Intestinal absorption of miscellaneous drugs

No.	Compound	log C (Eq. 31)		Clog P
		Obsd.	Pred.	
1	Atenolol	0.13	0.93	−0.11
2	Ciprofloxacin	0.66	0.47	−0.73
3	Foscarnet	−1.24	−0.62	−2.17
4	Mannitol	−0.85	−0.52	−2.05
5	Nordiazepam	2.29	1.98	3.02
6	Olsalazine	−2.17	−2.15	5.17
7	Oxazepam	2.11	2.37	2.31
8	Oxprenolol	2.11	2.34	2.09
9	Phenazone	2.11	1.16	0.20
10	Practolol	1.95	1.56	0.76
11	Raffinose	−2.37	−2.98	−5.32
12[a]	Sulfasalazine	−1.49	−7.50	3.88
13	Tranexamic acid	0.17	−0.34	−1.80
14	Alprenolol	2.02	2.28	2.65
15	Diazepam	2.11	2.05	2.96
16	Lactulose	−2.33	−1.68	−3.59
17[a]	Metolazone	0.48	−3.50	2.06
18	Metoprolol	2.64	2.06	1.49
19	Pindolol	1.73	2.17	1.67

[a] Not used in the derivation of Eq. 31.

Table 24. 100% Increase in excretion of uric acid in gouty patients by 1,2-di(4-substituted phenyl)-4-Y-3,5-pyrazolidinediones **III**

No.	Y	X	X′	log 1/*C* (Eq. 32)		p*K*a
				Obsd.	Pred.	
1	C_4H_9	Cl	Cl	2.58	2.59	4.80
2	C_4H_9	OH	H	2.57	2.64	4.70
3	C_4H_9	H	H	2.53	2.73	4.50
4	$CH_2CH_2CHOHCH_3$	H	H	3.16	2.97	4.00
5	CH_2CH_2 SC_6H_5	H	H	3.23	3.02	3.90
6[a]	C_4H_9	NO_2	H	3.74	3.36	3.20
7	C_4H_9	SO_2Me	SO_2Me	3.57	3.64	2.60
8	$COCH_2C_6H_5$	OH	H	3.89	3.93	2.00

[a] Not used in the derivation of Eq. 32.

Intestinal absorption of miscellaneous drugs; Data from Norinder et al.[31] (Table 23)

$$\log C = 0.75(\pm 0.14)\ \mathrm{Clog}P - 2.94(\pm 0.65)\log(\beta \times 10^{\mathrm{Clog}P} + 1) + 1.01(\pm 0.32)$$
$$n = 17,\ r^2 = 0.922,\ s = 0.560,\ q^2 = 0.886 \quad (31)$$
$$\log \beta = -2.78$$
$$\textit{optimum}\ \mathrm{Clog}P = 2.31$$
$$\textit{outliers}\text{: sulfasalazine; metolazone}$$

The authors put the data from Palm et al.[32] in logarithmic form. Neither report gives details on how the drugs were administered.

3.9. Urinary excretion

100% increase in excretion of uric acid in gouty patients by 1,2-di(4-substituted)phenyl-4-Y-pyrazolidine diones **III**; Data from Bloom and Lauback[33] (Table 24)

Table 25. Minimum alveolar concentration of miscellaneous gaseous anesthetics for no response of 50% patients to incision

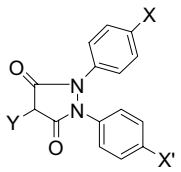
No.	Compound	log %*v*/*v* (Eq. 33)		log *P*
		Obsd.	Pred.	
1	$CHCl_3$	0.30	−0.02	1.97
2	Cyclopropane	−0.96	−0.34	1.72
3	Divinyl ether	−0.48	−0.14	2.82
4[a]	Ether	−0.28	−2.59	0.89
5	Ethrane	−0.23	−0.09	2.10
6	CH_3CH_2Cl	−0.30	−0.92	1.43
7	Ethylene	−1.83	−1.75	1.13
8	Fluroxene	−0.53	−0.26	1.77
9	Forane	−0.11	0.06	2.06
10[a]	Halopropane	0.30	−0.65	1.55
11	Halothane	−2.48	−2.59	0.89
12	Krypton	−2.48	−2.59	0.89
13	Methoxyflurane	0.80	0.14	2.21
14	Nitrogen	−3.36	−3.49	0.67
15[a]	Teflurane	−0.78	0.02	2.01
16	Trichloroethylene	0.70	0.16	2.29
17	Xenon	−1.85	−1.31	1.28

[a] Not used in the derivation of Eq. 33.

Table 26. Eosinopenic (anti-inflammatory) activity of glucocorticoids in man

No.	Compound	log AE (Eq. 34)		Clog *P*	NVE
		Obsd.	Pred.		
1	Cortisol	0.00	0.24	1.70	144
2	Coticosterone	−1.22	−0.79	2.32	138
3	Prednisolone	0.60	0.30	1.38	142
4	6-Me-11-OH-progesterone	−1.30	−1.45	3.17	138
5	6-Me-9-F-21-deoxycortisol	0.30	0.25	2.39	150
6	6-Me-prednisolone	0.70	0.60	1.70	148
7	6-Me-9-F-prednisolone	1.00	1.27	1.55	154
8	6-Me-9-F-21-deoxyprednisolone	0.30	0.31	2.07	148
9[a]	6-Me-16-OH-prednisolone	0.00	1.58	1.14	154
10	6-F-cortisol	0.60	0.75	1.74	150
11	6-F-prednisolone	0.95	0.81	1.43	148
12[a]	6,9-Di-F-16-OH-prednisolone	0.70	2.46	0.71	160
13	9-F-16-Me-prednisolone	1.08	1.11	1.75	154
14	6,9-Di-F-16-Me-prednisolone	1.48	1.63	1.79	160
15	9-F-cortisol	0.90	0.81	1.54	150
16	9-F-prednisolone	1.30	0.97	1.23	148
17	9-F-21-deoxy-prednisolone	−0.30	0.01	1.75	142
18[a]	9-F-16-OH-prednisolone	0.70	1.95	0.67	154
19	9-F-16-Me-21-deoxy-prednisolone	0.70	0.16	2.27	148

[a] Not used in the derivation of Eq. 34.



III

$$\log 1/C = -0.48(\pm 0.16)\ \mathrm{p}Ka + 4.89(\pm 0.62)$$
$$n = 7,\quad r^2 = 0.924,\quad s = 0.162,\quad q^2 = 0.881 \qquad (32)$$
$$\textit{outlier}:\ \mathrm{X} = \mathrm{NO_2},\ \mathrm{X}' = \mathrm{H},\ \mathrm{Y} = \mathrm{C_4H_9}$$

Hydrophobic character plays no role in the process. Thus more ionized compounds are more effective.

3.10. Anesthetic potency

Minimum alveolar concentration of miscellaneous gaseous anesthetics for no response to incision of 50% of patients; Data from Steward et al.[34] (Table 25)

$$\log \%v/v = 6.13(\pm 2.5)\log P - 1.31(\pm 0.72)\log P^2 - 7.01(\pm 2.00)$$
$$n = 14,\quad r^2 = 0.885,\quad s = 0.452,\quad q^2 = 0.759$$
$$\textit{optimum}\ \log P = 2.34\ (2.1\text{–}3.2)$$
$$\textit{outliers}\text{: ether; halopropane; teflurane} \qquad (33)$$

It is most interesting that the optimum $\log P$ is that for optimum CNS penetration.[19]

3.11. Eosinopenic potency

Eosinopenic (anti-inflammatory) potency of steroids in man; Data from Ahmad and Mellors[35] (Table 26)

$$\log \mathrm{AE} = -0.78(\pm 0.35)\ \mathrm{Clog}P + 0.09(\pm 0.03)\ \mathrm{NVE} - 11.6(\pm 4.8)$$
$$n = 16,\quad r^2 = 0.897,\quad s = 0.278,\quad q^2 = 0.836$$
$$\textit{outliers}\text{: 6-Me-16-OH-Prednisolone; 6,9-di-F-16-OH-Prednisolone; 9-F-16-OH-Prednisolone} \qquad (34)$$

NVE is the number of valence electrons (e.g., H = 1, C = 4, N = 5, O = 6, P = 5, S = 6, halogen = 7) summed for all atoms in a molecule. We have found this parameter to be especially important in the inhibition of nerve processes. By using the more familiar parameter CMR in place of NVE, yields r^2 of 0.823 and q^2 of 0.739. Both parameters are measures of molecular polarizability.

3.12. LD_{100} for man

King[36,37] made a first report on the concentration of various drugs necessary to kill 100% of those exposed. In England, when a person commits suicide or dies from an overdose of drugs, the concentration of the drug in the blood is determined. From these results we derived Eq. 35 (Table 27).

$$\log 1/C = 0.61(\pm 0.16)\log P + 0.02(\pm 0.004)\ \mathrm{NVE} + 1.45(\pm 0.36)$$
$$n = 37,\quad r^2 = 0.852,\quad s = 0.432,\quad q^2 = 0.820$$
$$\textit{outliers}\text{: morphine; theophylline; dichlorodifluoromethane; halothane} \qquad (35)$$

From the results in Table 27, one can choose his/her escape from this mad world!

3.13. Hallucinogenic activity

The data in Table 28 for testing of hallucinogenic compounds on humans came from the audacious work of

Table 27. LD_{100} for humans

No.	Compounds	log 1/C (Eq. 35)		log P	NVE
		Obsd.	Pred.		
1[a]	Morphine	5.45	3.46	0.15	110
2	Chlorpromazine	5.24	5.32	3.22	110
3	Propoxyphene	5.08	5.22	2.36	134
4	Strychnine	4.57	4.10	0.68	128
5	Quinine	4.45	4.93	2.11	126
6	Maprotiline	4.74	4.20	1.42	108
7	Pentazocine	4.50	4.68	2.04	114
8	Dothiepin	4.75	5.01	2.76	108
9	Flurazepam	4.86	5.35	2.35	142
10	Amitriptyline	4.92	4.85	2.50	108
11	Nortriptyline	4.24	4.27	1.71	102
12	Cocaine	4.70	4.15	1.05	118
13	Secobarbital	4.14	4.29	1.97	94
14	Desipramine	4.15	4.14	1.45	104
15	Propranolol	4.46	3.95	1.18	102
16	Diazepam	4.20	4.89	2.80	100
17	Phenobarbital	3.71	3.68	1.14	88
18	Chlormethiazole	3.51	3.61	2.12	50
19[a]	Theophylline	3.51	2.63	−0.02	68
20	Caffine	3.23	2.70	−0.07	74
21	Tetrachloroethylene	4.56	4.14	3.40	36
22[a]	Dichlorodifluoromethane	4.61	3.32	2.16	32
23	Toluene	4.34	3.73	2.73	36
24	Tetrachloromethane	3.14	3.72	2.83	32
25	1,1,1-Trichloroethane	3.22	3.52	2.49	32
26	Trichloroethylene	3.91	3.44	2.42	30
27	Trichlorofluoromethane	4.06	3.54	2.53	32
28	Nitrous oxide	2.39	1.99	0.43	16
29	Benzene	3.99	3.27	2.13	30
30	Diflurochloromethane	2.37	2.56	1.08	26
31[a]	Halothane	2.68	3.61	2.30	44
32	1,2-Dichloroethane	2.49	2.80	1.48	26
33	Chloroform	3.60	3.10	1.97	26
34	Bromochloromethane	2.81	2.65	1.41	20
35	Dichloromethane	2.37	2.56	1.25	20
36	Ethylchloride	2.21	2.67	1.43	20
37	Paraldehyde	2.88	2.80	0.67	54
38	Ether	2.17	2.55	0.89	32
39	Butanol	2.19	2.54	0.88	32
40	Isopropanol	1.26	1.94	0.05	26
41	Ethanol	1.26	1.83	0.05	20

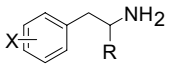
[a] Not used in the derivation of Eq. 35.

Table 28. Hallucinogenic activity of X-$C_6H_4CH_2CH(R)NH_2$ **[IV]**

	X	R	log RBR (Eq. 36)		log *P*	σ
			Obsd.	Pred.		
1	3,4,5-Tri-OMe	H	0.00	0.06	1.18	−0.03
2	3,4,5-Tri-OMe	Me	0.34	0.64	1.48	−0.03
3	2,4-Di-OMe	Me	0.70	0.55	1.75	−0.54
4	4-OMe	Me	0.70	0.86	1.77	−0.27
5	2,5-Di-OMe	Me	0.90	1.14	1.88	−0.15
6[a]	2,4,5-Tri-OMe	Me	1.23	0.66	1.74	−0.42
7	2,5-Di-OMe, 4-Me	Me	1.90	1.39	2.08	−0.15
8	2,5-Di-OMe, 4-C_3H_7	Me	1.85	1.80	3.31	−0.28
9	2,5-Di-OMe, 4-C_4H_9	Me	1.49	1.51	3.81	−0.31
10	2,5-Di-OMe, 4-C_2H_5	Me	1.98	1.75	2.81	−0.30
11	2,5-Di-OMe, 4-Br	Me	2.49	2.05	2.58	0.08
12	3-OCH_2O-4	Me	0.48	0.84	1.68	−0.16
13[a]	3-OMe, 4-OCH_2O-5	Me	0.43	1.15	1.80	−0.04
14	2-OMe, 4-OCH_2O-5	Me	1.08	1.41	2.42	−0.43
15	2-OMe, 3-OCH_2O-4	Me	1.00	1.05	2.04	−0.43
16	2-OCH_2O-3, 4-OMe	Me	0.48	0.62	1.72	−0.43
17	2,5-Di-OMe, 3-OCH_2O-4	Me	1.08	1.31	2.16	−0.31
18[a]	2,3-Di-OMe, 4-OCH_2O-5	Me	0.70	1.62	2.54	−0.31
19	3-OCH_2O-4	H	0.00	0.33	1.38	−0.16
20	2,3,5-Tri-OMe	Me	0.60	0.87	1.61	−0.03
21	2,3,4,5-Tetra-OMe	Me	0.78	0.36	1.48	−0.30
22	2,3,6-Tri-OMe	Me	1.10	0.65	1.73	−0.42
23	2,5-Di-OMe, 4-OC_2H_5	Me	1.18	0.30	2.24	−0.39
24	2,5-Di-OMe, 4-C_5H_{11}	Me	0.90	1.00	4.31	−0.30
25	3,4-Di-OMe	Me	0.00	−0.46	1.00	−0.15
26	2,3,4-Tri-OMe	Me	0.00	0.02	1.36	−0.42

[a] Not used in the derivation of Eq. 36.

Shulgin.[38] This work was completed at the University of Chile and published in the English journal *Nature*, since it would have been illegal in the United States. Analogs of mescaline (**IV**) were studied. See Table 28.



IV

$$\log \mathrm{RBR} = 3.39(\pm 0.93)\log P - 0.55(\pm 0.18)\log P^2 + 1.04(\pm 0.88)\sigma - 3.15(\pm 1.07)$$
$$n = 23, \quad r^2 = 0.822, \quad s = 0.310, \quad q^2 = 0.724$$
$$\textit{optimum} \ \log P = 3.1 \ (2.9\text{–}3.40) \qquad (36)$$

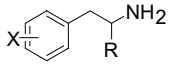
See Table 28 for three outliers.

How one can define a standard degree of hallucinogenicity in humans came about through years of study with many different subjects.[3,4] It is interesting that a weak term (σ) is present in Eq. 36. RBR is the relative biological activity compared to mescaline. Among other things, Shulgin et al. were interested in a possible relationship between hallucinogenicity and schizophrenia.

A second larger data set of mescaline analogs active in humans has been more recently published.[39] We have been guided by the results of Eq. 36. The electrotopological parameters yield great r^2 values, but it is not possible to compare one such QSAR with any other.

3.14. Psychomimetric activity of mescaline analogs (IV)

Relative potency in human. Data from Mracec et al.[39] (Table 29)



IV

$$\log \mathrm{MU} = 0.86(\pm 0.31)\sigma^+ + 0.39(\pm 0.14)B5_5 - 0.49(\pm 0.14)L_3 + 0.73(\pm 0.29)I + 1.90(\pm 0.80) \qquad (37)$$
$$n = 39, \ r^2 = 0.873, \ s = 0.292, \ q^2 = 0.828$$
$$I = 1 \text{ for 2-OMe}$$

See Table 29 for four outliers.

MU is the ratio of the effective dose of mescaline to the effective dose of the tested compounds.

One might have expected Eq. 37 to be similar to 36. They both contain Hammett parameters albeit different. The surprising major difference is the lack of hydrophobic terms in Eq. 37. This is unprecedented in our experience. The statistics are reasonable for Eq. 37, despite the fact that the data was collected from three different sources. Two commonly used 'recreational' chemicals are mescaline (compound 1 in Table 28) and ecstasy. All of these chemicals are derivatives of phenethylamine.

Table 29. Pyschomemetio activity of X-$C_6H_4CH_2CH(R)NH_2$ **[IV]**

No.	X	R	log MU (Eq. 37)		Clog *P*	$\sigma+$	$B5_5$	L_3	*I*
			Obsd.	Pred.					
1	2,5-Di-OMe, 4-I	Me	2.78	2.36	2.66	−0.52	3.07	2.06	1
2	2,5-Di-OMe, 4-Br	Me	2.72	2.37	2.45	−0.51	3.07	2.06	1
3	2,5-Di-OMe, 4-SCH_2CH_3	Me	1.96	1.72	2.44	−1.26	3.07	2.06	1
4	2,5-Di-OMe, 4-CH_2CH_3	Me	2.02	1.98	2.78	−0.96	3.07	2.06	1
5	2,5-Di-OMe, 4-$(CH_2)_2CH_3$	Me	1.95	1.99	3.31	−0.95	3.07	2.06	1
6	3,5-Di-OMe, 4-Br	Me	1.91	2.20	2.22	0.39	3.07	3.98	0
7	2,5-Di-OMe, 4-Me	Me	1.90	1.97	2.25	−0.97	3.07	2.06	1
8	2,5-Di-OMe, 4-$SCHMe_2$	Me	1.71	1.72	2.75	−1.26	3.07	2.06	1
9[a]	2,5-Di-OMe, 4-Br	H	1.69	2.37	2.14	−0.51	3.07	2.06	1
10	2,5-Di-OMe, 4-$(CH_2)_3CH_3$	Me	1.68	1.99	3.84	−0.95	3.07	2.06	1
11	2,5-Di-OMe, 4-SMe	Me	1.66	1.72	1.91	−1.26	3.07	2.06	1
12	3,5-Di-OMe, 4-SCH_2CH_3	H	1.36	0.82	1.73	−0.36	3.07	3.98	0
13	2,4,5-Tri-OMe	Me	1.33	1.57	1.39	−1.44	3.07	2.06	1
14[a]	2,5-Di-OMe, 4-CH_2CH_3	H	1.25	1.98	2.47	−0.96	3.07	2.06	1
15	3,5-Di-OMe, 4-$S(CH_2)_2CH_3$	H	1.29	0.99	2.66	−1.26	3.07	2.06	0
16[a]	2,5-Di-OMe, 4-Me	H	1.27	1.97	1.94	0.97	3.07	2.06	1
17	2,5-Di-OMe, 4-OCH_2CH_3	Me	1.36	1.54	1.91	−1.47	3.07	2.06	1
18	3,5-Di-OMe, 4-SMe	H	1.11	0.82	1.20	−0.36	3.07	3.98	0
19[a]	2,5-Di-OMe, 4-$(CH_2)_4CH_3$	Me	1.10	1.98	4.37	−0.96	3.07	2.06	1
20	3,5-Di-OMe, 4-OCH_2CH_3	Me	1.05	0.64	1.56	−0.57	3.07	3.98	0
21	2,5-Di-OMe, 4-$O(CH_2)_2CH_3$	Me	1.38	1.52	2.44	−1.49	3.07	2.06	1
22	3,5-Di-OMe, 4-OCH_2CH_3	H	0.87	0.64	1.26	−0.57	3.07	3.98	0
23	2,3,4,5-Tetra-OMe	Me	0.86	0.73	0.98	−1.32	3.07	3.98	1
24	3,5-Di-OMe, 4-$O(CH_2)_2CH_3$	H	0.83	0.62	1.78	−0.59	3.07	3.98	0
25	3,4-Di-OMe, 5-SCH_2CH_3	H	0.84	1.07	1.78	−0.48	3.97	3.98	0
26	3-OMe, 4-OCH_2CH_3, 5-SMe	H	0.84	0.74	1.78	−0.54	3.26	3.98	0
27	3,4-Di-OMe, 5-SMe	H	0.81	0.77	1.25	−0.57	3.26	3.98	0
28	3-OCH_2CH_3, 4-SMe, 5-OMe	H	0.66	0.40	1.73	−0.38	3.07	4.80	0
29	3-OCH_2CH_3, 4-SCH_2CH_3, 5-OMe	H	0.68	0.40	2.26	−0.38	3.07	4.80	0
30	2,4-Di-OMe	Me	0.67	0.66	1.75	−1.56	1.00	2.06	1
31	4-OMe	Me	0.59	0.60	1.66	−0.78	1.00	2.06	0
32	3,5-Di-OMe, 4-$S(CH_2)_3CH_3$	H	0.58	0.82	2.79	−0.36	3.07	3.98	0
33	3,5-Di-OMe, 4-$OCH_2C_6H_5$	Me	0.46	0.77	2.80	−0.42	3.07	3.98	0
34	3,5-Di-OMe, 4-$O(CH_2)_3CH_3$	H	0.38	0.64	2.31	−0.57	3.07	3.98	0
35	3-SCH_2CH_3, 4-OCH_2CH_3, 5-OMe	H	0.38	0.11	2.31	−0.51	3.07	5.16	0
36	3,4-OCH_2CH_3, 5-SMe	H	0.38	0.77	1.25	−0.51	3.26	3.98	0
37	3,4,5-Tri-OMe	Me	0.33	0.67	1.04	−0.54	3.07	3.98	0
38	3,4-OCH_2CH_3, 5-OMe	H	0.23	0.22	1.78	−0.59	3.07	4.80	0
39	3-OCH_2CH_3, 4,5-di-OMe	H	0.03	0.25	1.26	−0.56	3.07	4.80	0
40	3,4,5-Tri-OMe	H	0.00	0.67	0.73	−0.54	3.07	3.98	0
41	2,3,4-Tri-OMe	H	−0.03	−0.17	0.73	−1.44	1.00	3.98	1
42	3,4-Di-OMe	Me	−0.06	−0.24	1.40	−0.66	1.00	3.98	0
43	3,4-Di-OMe	H	−0.67	−0.24	1.09	−0.66	1.00	3.98	0

[a] Not used in the derivation of Eq. 37.

4. Conclusions

The results of our survey have shown that equations for the effect of chemicals in human can shed light on the current interest in absorption, distribution, metabolism and elimination (ADME). The presence of log *P* (both positive and negative terms) is clearly an important factor. We have long been interested in absorption. Albumin has received considerable attention. Our database contains 49 equations that contain log *P* terms for binding of a wide variety of chemicals to albumin. We have 52 equations that contain log *P* terms for the hemolysis of erythrocytes. Some of these results have been reviewed (Ref. 5, p 173, 419). Since binding of drugs by both albumin and erythrocytes is so similar we have long wondered how they would be distributed between the two systems. The best study we know of on distribution is that of Nestorov et al.[40] They studied the binding of a set of nine barbiturates to 15 different tissues in rats (e.g., lung, liver, kidney, heart, brain, etc.). All were log *P* dependent. The intercepts of these equations varied from −1.79 for plasma to 0.25 for liver. All of the equations were linear. Liver had the strongest affinity for the barbiturates and plasma had the weakest.

Metabolism presents the most complicated problem. Many chemicals induce the formation of Cytochrome P-450. We have long been concerned with this problem (Ref. 5, pp. 299–343) and recently reviewed the activity of Cytochrome P-450 in terms of QSAR.[41] We have found that the induction, inhibition and metabolic activity of Cytochrome P-450 are dependent on hydrophobic interactions. It is difficult to generalize on these problems except to say that hydrophobic interactions are important, but whether or not induction will overshadow metabolism is not clear. There is rela-

tively little QSAR work on the excretion of drugs in the urine.

Some time ago we tried to get some feeling for the ideal rate of CNS penetration of quite miscellaneous sets of CNS drugs.[19] A bar graph of 41 drugs showed that the largest number had log *P* values in the range of 1.2–2.4, no doubt other properties are associated with potency, etc. This is an attempt to get an overall feeling for ADME. Drugs with high log *P* tend to show more nonspecific toxicity and also tend to undergo microsomal oxidation that not only results in drug loss, but may yield toxic products. Drugs with low log *P* will tend to be more readily excreted in the urine.

In conclusion, we can say that QSAR for ADME can be formulated for the various types of experiments in human system.

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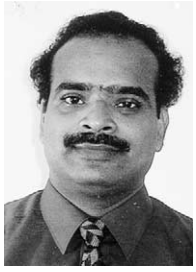
Biographical sketch



Rajeshwar Prasad Verma was born in 1966 in Barh (India). He received his M.Sc. (1988), and Ph.D. (1992) degrees in Chemistry from Magadh University, Bodh-Gaya. He spent a year at the same university as a postdoctoral fellow with Professor K. S. Sinha. He joined Roorkee University (Now IIT Roorkee) as a research associate and worked with Professor S. M. Sondhi (1993–1997). He also worked as a Lecturer of Chemistry at Gurukula Kangri University, Hardwar (1994–1995). He won a Research Associateship Award in December 1994 from the Council of Scientific & Industrial Research, New Delhi (India). In 1997, he moved to Pomona College to join the renowned QSAR research group of Professor Corwin Hansch & Cynthia Selassie and working as a postdoctoral research associate. Dr, Verma's research interest include the following: Isolation, characterization, and synthesis of natural products derived from medicinal plants; chemistry of isothiocyanates; synthesis of biologically important heterocycles and phenolic/active hydrogen compounds; application of principles of quantitative structure activity relationships (QSAR) to the study of antifolates, multidrug resistance, freeradical-mediated toxicity of phenolic/active hydrogen compounds and computer-assisted drug design.

Alka Kurup received her undergraduate degree in Pharmacy in 1981 from Birla Institute of Technology and Science, Pilani, India. She received her Masters degree in Medicinal Chemistry from the College of Pharmacy, Manipal, India in 1988. For two years she assumed Incharge-ship and Quality Control of the Pharmacy Manufacturing Wing at Kasturba Medical College Hospital in Manipal. In 1991, she joined Birla Institute of Technology and Science, Pilani as faculty in the Department of Pharmacy. She completed her PhD in 1997 under the supervision of Professor S. P. Gupta with her thesis regarding QSAR studies of anticancer drugs. She joined Professor Corwin Hansch's group in July 1998 to pursue postdoctoral research. At present she is working at Biobyte Corp. as senior research scientist. Her research interests include QSAR and Computer aided drug design.

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Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in organic chemistry form New York University in 1944. After working with the Du Pont Co., first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich, Switzerland, with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.