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Structure-activity relationships of volatile organic chemicals as sensory irritants

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Abstract We used a database of 145 volatile organic chemicals for which the sensory irritation potency (RD_{50}) has been reported in mice. Chemicals were first separated into two groups: nonreactive and reactive, using Ferguson's rule. This rule suggests that nonreactive chemicals induce their effect via a physical (*p*) mechanism (i.e., weak forces or interactions between a chemical and a biological receptor). Therefore, appropriate physicochemical descriptors can be used to estimate their potency. For reactives, a chemical (*c*) mechanism (i.e., covalent bonding with the receptor) would explain their potency. All chemicals were also separated on the basis of functional groups and subgroups into 24 classifications. Our results indicated that the potency of nonreactive chemicals, regardless of their chemical structure, can be estimated using a variety of physicochemical descriptors. For reactive chemicals, we identified five basic reactivity mechanisms which explained why their potency was higher than that estimated from physicochemical descriptors. We concluded that Ferguson's proposed rule is adequate initially to classify two separate mechanisms of receptor interactions, *p* vs *c*. Several physicochemical descriptors can be used to estimate the potency of *p* chemicals, but chemical reactivity descriptors are needed to estimate the potency for *c* chemicals. At present, this is the largest database for nonreactive-reactive chemicals in toxicology. Because of the wide variety of *c* chemicals presented, a semi-quantitative estimate of the potency of new, or not previously evaluated, *c* chemicals can be arrived at via comparison with those presented and the basic chemical reactivity mechanisms presented.

Key words Sensory irritation · Structure activity relationship · Quantitative structure-activity relationships, QSAR

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Introduction

In 1939, Ferguson proposed two main mechanisms for some acute toxic effects of vapors, depending upon the type of their interaction with biological receptors. A physical mechanism (*p*) was proposed for the interaction of nonreactive volatile organic chemicals. This mechanism would include the forces for all types of weak noncovalent bonds: electrostatic interactions, hydrogen bonds, van der Waals attractions, and hydrophobic forces with a biological receptor. This mechanism was shown to be valid for nonreactive vapors acting as sensory irritants (Abraham et al. 1990, 1994; Alarie et al. 1995, 1996). These studies also revealed that an increase in sensory irritation potency, measured as the RD_{50} in mice, was obtained by an increase in dipolarity/polarizability, overall hydrogen-bond acidity, and lipophilicity of nonreactive volatile chemicals (Abraham et al. 1990, 1994). Lipophilicity was found to be the most important contributor. Also, confirming the original observation of Ferguson, these studies showed an increase in potency with decreasing vapor pressure of the volatile nonreactive chemicals investigated. The potency ($\log RD_{50}$) was positively correlated with their Ostwald solubility coefficient on olive oil [$\log L(Oil)$; i.e., lipophilicity] and equally negatively correlated with their vapor pressure ($\log P^o$). This was shown for a group of 59 nonreactive organic chemicals belonging to various chemical classes (Alarie et al. 1995) and for a group of 76 organic chemicals, including some with slight chemical reactivity (Alarie et al. 1996).

A chemical mechanism (*c*) was proposed for the interaction of volatile organic reactive chemicals. This

mechanism would include all covalent or ionic binding mechanisms, reversible or nonreversible, with the receptor. For these chemicals, their potency should not be directly correlated with their lipophilicity or vapor pressure (Ferguson 1939). However, lipophilicity must still play a role for these chemicals reaching the receptor (Abraham et al. 1994). In a recent analysis, it was suggested that the potency of a varied set of nonreactive chemicals could be understood on the basis of simple physical (or passive) transfer to the site of action or passive transfer plus interactions with receptors (Abraham et al. 1994). The potency was then related to physicochemical descriptors, such as vapor pressure, or the Ostwald solubility coefficient in a solvent like olive oil. This is the basis of the Ferguson rule. If other mechanisms take place, such as reaction with a component of a biological system, then simple general relationships between potency and vapor pressure or potency and vapor solubility break down. We can thus identify the *p* and *c* mechanisms, as given above. The *p* mechanism will be dominated by passive transport and physical interactions; the *c* mechanism will include these effects, because the chemical must still reach the site of action, plus a reactivity component as well. A wide variety of reactive sensory irritants exists. For two homologous series of reactive sensory irritants evaluated as aerosols, it has been shown that their potency was highly correlated with their reactivity towards a nucleophilic group such as SH (Alarie 1973a; Tarantino and Sass 1974). Also, a wide variety of reactive sensory irritants can react with an SH group (Alarie 1973b). Thus both *p* and *c* chemicals have been identified as sensory irritants (Alarie 1973b). Since both physical and chemical interactions can be equally important in biological receptor systems (for examples, see Alberts et al. 1994), formulation of a receptor to accommodate both types of interaction for sensory irritants was proposed by Nielsen (1991).

There is an obvious difficulty (i.e., some subjectivity) in defining nonreactive vs reactive chemicals in a biological system. In previous reports, the term 'nonreactive' was used to describe a variety of chemicals commonly used as solvents (Nielsen and Alarie 1982; Abraham et al. 1990, 1994; Alarie et al. 1995, 1996) and as noted above, the term 'reactive' was used to indicate reactivity towards a nucleophilic group. We will retain this general nonreactivity-reactivity concept in this article, although Ferguson did not use this approach. Instead, he separated the two groups on the basis of the ratio of the vapor concentration in air to induce a given toxicological effect/the saturated vapor concentration of the investigated chemicals. Chemicals with a ratio >0.1 were proposed to act via a physical mechanism (*p*) while those with a ratio <0.1 were proposed to act via a chemical mechanism (*c*). Very few of the latter were listed by Ferguson. Therefore, it is difficult to judge the adequacy of his proposition. Nevertheless, we will retain the *p* vs *c* concept in this article using the same basis given by Ferguson initially to classify each investigated chemical in the database. After using Ferguson's rule to separate *p* vs *c* chemicals, we will then attempt to verify whether or not this rule can be supported using basic principles of organic chemistry to classify reactive vs nonreactive chemicals. With a large database of nonreactive and reactive volatile organic chemicals acting as sensory irritants (Schaper 1993), we can evaluate whether or not Ferguson's proposition (i.e., ratios >0.1 or <0.1) is appropriate, as well as how large a difference in potency can be found between nonreactive and reactive chemicals. The analysis presented should also stimulate the formulation of adequate descriptors for 'reactivity' for future formulation of quantitative reactivity-potency analysis as is available to estimate the sensory irritating potency for nonreactive chemicals from physicochemical descriptors (Abraham et al. 1990, 1994; Alarie et al. 1995).

Materials and methods

Chemicals selected

Database and physicochemical variables

We used the database of Schaper (1993) which listed the sensory irritating potency obtained in mice (RD_{50} values) for 244 chemicals. From this database, we selected the organic chemicals and only those evaluated as vapors, thus excluding all chemicals evaluated as aerosols. This yielded a total of 145 chemicals, alphabetically listed in Table 1. For each chemical, the RD_{50} value is given as well as the values for the physicochemical properties previously used for analysis of nonreactive chemicals (Abraham et al. 1990, 1994; Alarie et al. 1995, 1996). These are:

R_2, excess molar refraction;
π_2^H, chemical dipolarity/polarizability;
$\Sigma\alpha_2^H$, chemical overall or effective hydrogen-bond acidity;
$\Sigma\beta_2^H$, chemical overall or effective hydrogen-bond basicity;
$\log L^{16}$, chemical Ostwald partition coefficient on hexadecane at 25 °C;
log L (Oil), chemical Ostwald partition coefficient on olive oil at 30 °C; and
$\log P^o$, chemical vapor pressure at 22–25 °C

The Ostwald partition coefficients (L) noted above are given for each chemical (or solute) as: concentration of solute in solvent/concentration of solute in the gas phase. The RD_{50} value listed for each chemical in Table 1 was obtained in male Swiss-Webster, OF1, or CF1 mice. When multiple values were reported in these mice for a particular chemical (Schaper 1993), an average value was calculated, as given in Table 1.

p vs c chemicals or nonreactive vs reactive chemicals

The chemicals in the database were classified according to two possible mechanisms of action: *p* for what should be nonreactive chemicals or *c* for what should be reactive chemicals, following the rule proposed by Ferguson noted above. Thus, a chemical is listed as *p* in Table 1 if the ratio $P^{RD\,50}/P^o$ was found to be >0.1, ($P^{RD\,50}$ being the RD_{50} exposure concentration and P^o the vapor pressure at 22–25 °C, units for both in mm Hg or in ppm). A chemical is listed as *c* in Table 1 when $P^{RD\,50}/P^o$ was <0.1. In this manner, a total of 59 *p* (or nonreactive) and 83 *c* (or reactive) chemicals were obtained. The letter, *c* or *p*, is listed for each chemical in Table 1. Our first objective is to contrast these two sets of chemicals. Three chemicals were unclassified (*u*). These were: allyl ether, cyclohexane

Table 1 Physicochemical properties and sensory irritation potency of organic volatile chemicals[a]

No.	Chemical[b]	C[c]	CAS[d] no.	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	log L^{16}	log L (Oil)	log P^o (mm Hg)	log RD_{50} (ppm)
1	Acetaldehyde	F *c*	75-07-0	0.208	0.67	0.00	0.45	1.230	1.40	2.9592[e]	3.591
2	Acetic acid	C *c*	64-19-7	0.265	0.65	0.61	0.44	1.750	2.68	1.1872[f]	2.568
3	Acetone Propan-2-one	N *p*	67-64-1	0.179	0.70	0.04	0.49	1.696	1.92	2.3637[f]	4.703
4	Acetophenone	U *p*	98-86-2	0.818	1.01	0.00	0.48	4.501	4.58	−0.4685[e]	2.009
5	Acrolein	G *c*	107-02-8	0.324	0.72	0.00	0.45	1.656	1.82	2.4387[e]	0.318
6	Allyl iodide	L *c*	556-56-9	0.800	0.64	0.00	0.05	3.010	2.96	1.5911[g]	1.838
7	Allyl acetate	B *c*	591-87-7	0.199	0.72	0.00	0.49	2.723	2.76	1.5571[i]	0.462
8	Allyl alcohol	E *c*	107-18-6	0.342	0.46	0.38	0.48	1.951	2.39	1.3978[f]	0.439
9	Allyl amine	I *c*	107-11-9	0.350	0.49	0.16	0.58	2.268	2.39	2.3740[e]	0.954
10	Allyl bromide	L *c*	106-95-6	0.427	0.60	0.00	0.07	2.510	2.48	2.1449[e]	2.332
11	Allyl chloride	L *c*	107-05-1	0.327	0.56	0.00	0.05	2.109	2.09	2.5658[f]	3.241
12	Allyl ether	K *u*	557-40-4	0.228	0.38	0.00	0.45	2.430	2.23		0.699
13	Allyl glycidyl ether	K *c*	106-92-3							0.3010[h]	0.756
14	*n*-Amylbenzene *n*-Pentylbenzene	R *p*	538-68-1	0.594	0.51	0.00	0.15	5.230	4.82	−0.4841[j]	2.362
15	Benzaldehyde	P *p*	100-52-7	0.820	1.00	0.00	0.39	4.008	4.13	0.0969[e]	2.522
16	Benzyl bromide	Q *c*	100-39-0	1.014	0.98	0.00	0.20	4.672	4.71	−0.1355[e]	0.716
17	Benzyl chloride	Q *c*	100-44-7	0.821	0.82	0.00	0.33	4.384	4.32	0.0806[e]	1.342
18	Benzyl iodide	Q *c*	620-05-3	1.361		0.00	0.21			−0.4949[g]	0.633
19	Bromobenzene	T *c*	108-86-1	0.882	0.73	0.00	0.09	4.041	4.14	0.6258[e]	2.613
20	2-Butoxyethanol	X *p*	111-76-2	0.201	0.50	0.30	0.83	3.806	3.96	0.0453[e]	3.451
21	*n*-Butyl acetate	A *c*	123-86-4	0.071	0.60	0.00	0.45	3.353	3.23	1.0597[f]	2.865
22	tert-Butyl acetate	A *p*	540-88-5	0.025	0.54	0.00	0.47	2.802	2.69	1.5809[g]	4.203
23	*n*-Butyl alcohol Butan-1-ol	D *p*	71-36-3	0.224	0.42	0.37	0.48	2.601	2.94	0.7954[f]	3.641
24	*n*-Butylamine	H *c*	109-73-9	0.224	0.35	0.16	0.61	2.618	2.59	1.9626[k]	2.066
25	tert-Butylamine	H *c*	75-64-9	0.121	0.29	0.16	0.71	2.493	2.43	2.5653[f]	2.250
26	*n*-Butylbenzene	R *p*	104-51-8	0.600	0.51	0.00	0.15	4.730	4.46	0.0128[j]	2.851
27	tert-Butylbenzene	R *p*	98-06-6	0.619	0.49	0.00	0.18	4.413	4.08	0.3314[j]	2.881
28	*p*-tert-Butyltoluene 4-t-Butyltoluene	R *p*	98-51-1	0.620	0.50	0.00	0.19	4.926	4.55	−0.1785[e]	2.556
29	Butyraldehyde	F *c*	123-72-8	0.187	0.65	0.00	0.45	2.270	2.30	2.0453[f]	3.006
30	Caproaldehyde	F *p*	66-25-1	0.160	0.65	0.00	0.45	4.361	4.16	0.3818[e]	3.624
31	Chlorobenzene	T *c*	108-90-7	0.718	0.65	0.00	0.07	3.657	3.46	1.0794[e]	3.023
32	Chloro-2-ethylbenzene 2-Chloroethylbenzene	Q *c*	622-24-2	0.801	0.90	0.00	0.25	4.600	4.58	−0.0297[f]	1.924
33	*o*-Chlorobenzylchloride	Q *c*	611-19-8	0.931	0.98	0.00	0.25	5.101	5.09	−0.8239[g]	0.756
34	*m*-Chlorobenzylchloride	Q *p*	620-20-2	0.940	0.88	0.00	0.25	5.000	4.92	−0.7878[g]	1.431
35	*p*-Chlorobenzylchloride	Q *c*	104-83-6	0.920	0.88	0.00	0.25	4.813	4.75	−0.7932[g]	1.146
36	Chloropicrin	X *c*	76-06-2	0.461	0.84	0.00	0.09			1.3967[e]	0.902
37	*o*-Chlorotoluene 2-Chlorotoluene	Q *p*	95-49-8	0.762	0.65	0.00	0.07	4.173	4.00	0.5494[e]	2.756
38	Crotonaldehyde	G *c*	4170-30-3	0.387	0.80	0.00	0.50	2.570	2.69	1.5758[f]	0.548
39	Crotyl alcohol	E *c*	6117-91-5	0.350	0.44	0.38	0.48	2.618	2.96	0.8579[h]	0.949
40	Cyclohexanone	N *p*	108-94-1	0.403	0.86	0.00	0.56	3.792	3.83	0.6024[e]	2.879
41	Cyclohexane carboxaldehyde	X *u*	2043-61-0			3.790					2.270
42	3-Cyclohexene 1-carboxaldehyde	X *c*	100-50-5							0.3010[h]	1.978
43	Cyclohexylamine	H *c*	108-91-8	0.326	0.56	0.16	0.58	3.796	3.81	0.9460[f]	1.591
44	Diallylamine	I *c*	124-02-7	0.329						1.3729[h]	0.602
45	Dibutylacetone Nonan-5-one	N *p*	502-56-7	0.103	0.66	0.00	0.51	4.698	4.47	−0.2596[l]	2.436
46	Dibutylamine	H *c*	111-92-2	0.107	0.30	0.08	0.69	4.349	3.98	0.3583[e]	2.104
47	1,2 Dichlorobenzene	T *p*	95-50-1	0.872	0.78	0.00	0.04	4.518	4.60	0.1146[f]	2.259
48	α,α-Dichlorotoluene	Q *c*	98-87-3	0.916	0.79	0.10	0.28	5.151	5.120	‘−0.3279[e]	1.301
49	Diethylamine	H *c*	109-89-7	0.154	0.30	0.08	0.69	2.395	2.24	2.3709[f]	2.286
50	Diisobutyl acetone 2,6 Dimethylheptan-4-one	N *p*	108-83-8	0.051	0.60	0.00	0.51	4.244	4.02	0.2345[e]	2.505
51	Diisopropylamine	H *c*	108-18-9	0.053	0.24	0.08	0.73	2.893	2.64	1.9054[e]	2.207
52	Dimethylamine	H c	124-40-3	0.189	0.30	0.08	0.66	1.600	1.54	3.1875[e]	2.463
53	3-Dimethylamino-1-propylamine	H *c*	109-55-7							1.0000[h]	2.246
54	Dimethylethylamine	H *c*	598-56-1	0.094	0.18	0.00	0.64	2.125	1.80	2.6812[g]	2.207
55	Dimethylisopropylamine	H *c*	996-35-0			0.00				1.0531[h]	1.954

(continued overleaf)

Table 1 (continued)

No.	Chemical[b]	C[c]	CAS[d] no.	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	log L^{16}	log L (Oil)	log P^o (mm Hg)	log RD_{50} (ppm)
56	Dipropylamine	H *c*	142-84-7	0.124	0.30	0.08	0.69	3.351	3.09	1.3820[e]	1.964
57	Divinyl benzene 1,4 Divinylbenzene	S *c*	1321-74-0	1.080	0.75	0.00	0.20	4.900	4.73	−0.1844[e]	1.892
58	2-Ethoxyethyl acetate	A *p*	111-15-9	0.099	0.79	0.00	0.79	3.747	3.73	0.2639[e]	2.857
59	Ethyl acetate	A *c*	141-78-6	0.106	0.62	0.00	0.45	2.314	2.36	1.9760[f]	2.776
60	Ethyl acrylate	X *c*	140-88-5	0.212	0.64	0.00	0.42	2.758	2.73	1.5860[e]	2.498
61	Ethyl alcohol Ethanol	D *p*	64-17-5	0.246	0.42	0.37	0.48	1.485	1.96	1.7714[f]	4.311
62	Ethylamine	H *c*	75-04-7	0.236	0.35	0.16	0.61	1.677	1.76	3.0183[f]	2.179
63	Ethylbenzene	R *p*	100-41-4	0.613	0.51	0.00	0.15	3.778	3.49	0.9781[j]	3.439
64	2-Ethyl-butyraldehyde	F *c*	97-96-1	0.140	0.62	0.00	0.45	3.180	3.09	1.3522[g]	2.926
65	Ethyl-2-hexanol 2-Ethylhexan-1-ol	D *p*	104-76-7	0.209	0.39	0.37	0.48	4.433	4.52	−0.8447[e]	1.643
66	Ethylidene norbornene	X *p*	16219-75-3	0.586	0.27	0.00	0.15	4.147	3.67	0.7619[e]	3.398
67	Formaldehyde	F *c*	50-00-0	0.220	0.70	0.00	0.33	0.730	1.42	3.5979[e]	0.628
68	2-Furaldehyde Furfural	P *c*	98-01-1	0.690	1.20	0.00	0.44	3.262	3.63	0.3711[e]	2.458
69	Heptane	M *p*	142-82-5	0	0.00	0.00	0.00	3.173	2.59	1.6601[j]	4.193
70	*n*-Heptanol Heptan-1-ol	D *p*	111-70-6	0.211	0.42	0.37	0.48	4.115	4.26	−0.7447[f]	1.993
71	Heptan-2-one	N *p*	110-43-0	0.123	0.68	0.00	0.51	3.760	3.60	0.5798[e]	2.951
72	Heptan-4-one	N *p*	123-19-3	0.113	0.66	0.00	0.51	3.705	3.59	0.0899[e]	3.041
73	Heptylamine	H *c*	111-68-2	0.197	0.35	0.16	0.61	4.166	3.97	0.4330[e]	1.425
74	Hexachloro-1,3-butadiene	L *p*	87-68-3	1.019	0.85	0.00	0.05			−0.9957[e]	2.324
75	1,6 Hexamethylene diisocyanate	V *c*	822-06-0							−1.6021[h]	−0.770
76	*n*-Hexanol Hexan-1-ol	D *p*	111-27-3	0.210	0.42	0.37	0.48	3.610	3.82	−0.1791[e]	2.378
77	*n*-Hexyl acetate	A *p*	142-92-7	0.056	0.60	0.00	0.45	4.351	4.11	0.1430[e]	2.869
78	Hexylamine	H *c*	111-26-2	0.197	0.35	0.16	0.61	3.655	3.51	0.9777[e]	1.703
79	*n*-Hexylbenzene	R *p*	1077-16-3	0.591	0.50	0.00	0.15	5.720	5.25	−0.9914[j]	2.097
80	Hexyl isocyanate	V *c*	2525-62-4							0.3541[g]	0.681
81	Isoamyl alcohol 3-Methylbutan-1-ol	D *p*	123-51-3	0.192	0.39	0.37	0.48	3.011	3.26	0.4594[e]	3.413
82	Isobutyl acetate	A *c*	110-19-0	0.052	0.57	0.00	0.47	3.161	3.03	1.2931[e]	2.913
83	Isobutyl alcohol 2-Methylpropan-1-ol	D *p*	78-83-1	0.217	0.39	0.37	0.48	2.413	2.74	1.0249[e]	3.260
84	Isobutylamine	H *c*	78-81-9	0.198	0.32	0.16	0.63	2.469	2.43	2.1535[e]	1.959
85	Isobutyraldehyde	F c	78-84-2	0.144	0.62	0.00	0.45	2.120	2.15	2.2369[f]	3.620
86	Isopentyl acetate Isoamylacetate	A *p*	123-92-2	0.051	0.57	0.00	0.47	3.740	3.55	0.7372[e]	3.024
87	Isophorone	O *c*	78-59-1	0.511	1.12	0.00	0.53			−0.3526[e]	1.444
88	Isopropyl acetate	A *c*	108-21-4	0.055	0.57	0.00	0.47	2.546	2.48	1.7803[e]	3.629
89	Isopropyl alcohol Propan-2-ol	D *p*	67-63-0	0.212	0.36	0.33	0.56	1.764	2.16	1.6308[m]	4.055
90	Isopropylamine	H *c*	75-31-0	0.183	0.32	0.16	0.61	1.908	1.94	2.7675[e]	2.196
91	Isopropylbenzene	R *p*	98-82-8	0.602	0.49	0.00	0.16	4.084	3.79	0.6613[j]	3.345
92	Isovaleraldehyde 3-Methylbutanal	F *c*	590-86-3	0.144	0.62	0.00	0.45	2.620	2.59	1.8195[g]	3.003
93	Menthol	X *c*	89-78-1	0.400	0.48	0.32	0.61			−0.0969[h]	1.653
94	Mesityl oxide	O *c*	141-79-7	0.412		0.00		3.300		1.0298[e]	1.786
95	2-Methoxyethyl acetate	A *c*	110-49-6	0.166	0.79	0.00	0.81	3.290	3.32	0.6920[i]	2.756
96	Methyl acetate	A *c*	79-20-9	0.142	0.64	0.00	0.45	1.911	2.02	2.3349[e]	2.919
97	Methyl alcohol Methanol	D *p*	67-56-1	0.278	0.44	0.43	0.47	0.970	1.47	2.1040[m]	4.523
98	Methylamine	H *c*	74-89-5	0.250	0.35	0.16	0.58	1.300	1.42	3.4209[f]	2.149
99	Methyl *n*-butyl acetone Hexan-2-one	N *p*	591-78-6	0.136	0.68	0.00	0.51	3.262	3.21	1.0626[e]	3.407
100	Methyl-tert-butylacetone 3,3 Dimethylbutan-2-one	N *p*	75-97-8	0.106	0.62	0.00	0.51	2.928	2.86	1.5052[f]	3.747
101	Methyl crotonate	X *c*	623-43-8	0.284						1.2553[h]	2.308
102	Methyl ethyl ketone Butan-2-one	N *p*	78-93-3	0.166	0.70	0.00	0.51	2.287	2.36	1.9565[f]	4.701
103	Methyl-5-heptan-3-one 5-Methylheptan-3-one	N *p*	541-85-5	0.110	0.63	0.00	0.51	4.200	4.00	0.2014[g]	2.880
104	Methyl-5-hexan-2-one 5-Methylhexane-2-one	N *p*	110-12-3	0.114	0.53	0.00	0.51	3.605	3.49	0.7612[g]	3.091

Table 1 (continued)

No.	Chemical[b]	C[c]	CAS[d] no.	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	log L^{16}	log L (Oil)	log P^o (mm Hg)	log RD_{50} (ppm)
105	Methylisobutylketone 4-Methylpentan-2-one	N *p*	108-10-1	0.111	0.65	0.00	0.51	3.089	2.97	1.2878[f]	3.504
106	Methyl isocyanate	V *c*	624-83-9	0.262		0.00				2.6541[e]	0.114
107	Methyl-4-pentan-2-ol 4-Methylpentan-2-ol	D *c*	108-11-2	0.167	0.33	0.33	0.56	3.179	3.30	0.7865[f]	2.628
108	α-Methyl styrene	S *c*	98-83-9	0.851	0.64	0.00	0.19	4.292	4.10	0.3851[e]	2.436
109	Methyl vinyl acetone Methyl vinyl ketone	O *c*	78-94-4	0.291	0.76	0.00	0.48	2.330	2.45	1.9562[e]	0.723
110	Nonane	M *p*	111-84-2	0	0.00	0.00	0.00	4.182	3.48	0.6314[j]	4.794
111	Octane	M *p*	111-65-9	0	0.00	0.00	0.00	3.677	3.04	1.1449[f]	4.259
112	*n*-Octanol Octan-1-ol	D *p*	111-87-5	0.199	0.42	0.37	0.48	4.619	4.71	−1.1249[f]	1.674
113	Octan-2-one	N *p*	111-13-7	0.108	0.68	0.00	0.51	4.257	4.09	0.1038[e]	2.680
114	*n*-Pentanol Pentan-1-ol	D *p*	71-41-0	0.219	0.42	0.37	0.48	3.106	3.38	0.2765[e]	3.366
115	Pentan-2-one	N *p*	107-87-9	0.143	0.68	0.00	0.51	2.755	2.70	1.5478[e]	3.773
116	*n*-Pentyl acetate	A *p*	628-63-7	0.067	0.60	0.00	0.45	3.844	3.48	0.6068[i]	3.179
117	Pentylamine	H *c*	110-58-7	0.211	0.35	0.16	0.61	3.139	3.05	1.4843[e]	1.987
118	Phenol	X *p*	108-95-2	0.805	0.89	0.60	0.30	3.766	4.29	−0.3947[e]	2.220
119	Phenyl isocyanate	W *c*	103-71-9							0.4336[e]	−0.137
120	3-Picoline 3-Methyl pyridine	X *p*	108-99-6	0.631	0.81	0.00	0.54	3.631	3.73	0.7784[f]	3.906
121	Propionaldehyde	F *c*	123-38-6	0.196	0.65	0.00	0.45	1.815	1.90	2.5020[e]	3.755
122	Propionic acid	C *c*	79-09-4	0.233	0.65	0.60	0.45	2.290	3.13	0.5205[f]	2.584
123	Propyl acetate	A *c*	109-60-4	0.092	0.60	0.00	0.45	2.819	2.78	1.5270[f]	2.899
124	*n*-Propyl alcohol Propan-1-ol	D *p*	71-23-8	0.236	0.42	0.37	0.48	2.031	2.50	1.3107[f]	4.016
125	*n*-Propylamine	H *c*	107-10-8	0.225	0.35	0.16	0.61	2.141	2.17	2.4996[e]	2.175
126	Propylbenzene *n*-Propylbenzene	R *p*	103-65-1	0.604	0.50	0.00	0.15	4.230	3.99	0.5272[j]	3.185
127	Propyl ether	J *p*	111-43-3	0.008	0.25	0.00	0.45	2.954	1.81	1.7959[e]	4.949
128	3-Pyridine carboxaldehyde	X *u*	500-22-1	0.817	1.16	0.00	0.76	4.258	4.48		2.740
129	Styrene	S *c*	100-42-5	0.849	0.65	0.00	0.16	3.856	3.68	0.8185[f]	2.759
130	Toluene	R *p*	108-88-3	0.601	0.52	0.00	0.14	3.325	3.08	1.4541[j]	3.656
131	2,4 Toluene diisocyanate	W *c*	584-84-9							−1.7696[e]	−0.699
132	2,6 Toluene diisocyanate	W *c*	91-08-7							−1.7212[e]	−0.585
133	*p*-Toluene isocyanate	W *c*	622-58-2							−0.0655[g]	−0.201
134	*o*-Toluene isocyanate	W *c*	614-68-6							−0.0969[g]	0.161
135	2,3,4 Trichloro-1-butene	L *c*	2431-50-7							1.3010[h]	1.764
136	Triethylamine	H *c*	121-44-8	0.101	0.15	0.00	0.79	3.040	2.83	1.8261[e]	2.233
137	2,2,2 Trifluoroethanol	X *p*	75-89-8	0.015	0.60	0.57	0.25	1.224	2.11	1.8692[e]	4.320
138	Trimethylamine	H *c*	75-50-3	0.140	0.20	0.00	0.67	1.620	1.37	3.2209[f]	1.785
139	Undecan-2-one	N *p*	112-12-9	0.101	0.68	0.00	0.51	5.732	5.40	−1.4318[l]	1.558
140	Valeraldehyde	F *c*	110-62-3	0.163	0.65	0.00	0.45	2.851	2.82	1.6278[g]	3.050
141	2-Vinylpyridine	X *c*	100-69-6			0.00				−0.1487[g]	1.407
142	4-Vinylpyridine	X *c*	100-43-6			0.00				−0.4437[g]	1.072
143	Vinyl toluene 4-Methyl styrene	S *c*	25013-15-4	0.871	0.65	0.00	0.18	4.399	4.20	0.2572[f]	1.215
144	*o*-Xylene	R *p*	95-47-6	0.663	0.56	0.00	0.16	3.939	3.64	0.8209[j]	3.166
145	*p*-Xylene	R *p*	106-42-3	0.613	0.52	0.00	0.16	3.839	3.53	0.9423[j]	3.122

[a] Values for the physical descriptors, except log P^o, are from Alarie et al. (1996) or calculated according to Abraham (1993). Values for log P^o are from the references given below. For definition of the physicochemical properties, see the Materials and methods

[b] Chemical name as listed in Schaper (1993), second name as previously used in Abraham et al. (1994) or Alarie et al. (1995)

[c] Chemicals as classified in Table 2, A to X, according to chemical groups and subgroups and classified as acting via a physical (*p*) or chemical (*c*) mechanism according to the rule given in text

[d] CAS no., Chemical Abstract Service number

[e] Stephenson and Malinowski (1987)

[f] Boublik et al. (1984)

[g] Estimated from measured values of related chemicals listed in this Table

[h] Schaper (1993)

[i] Riddick and Bunger (1970)

[j] Wilhoit and Zwolinski (1971)

[k] Dreisbach (1961)

[l] Ambrose et al. (1975)

[m] Ambrose and Sprake (1970)

Table 2 Groups and subgroups for the chemicals listed in Table 1

Chemical group and subgroup			Identifying letter in Table 1	Number of chemicals in group	Identifying number in Table 1
Aliphatic	Acetate	Saturated	A	12	21, 22, 58, 59, 77, 82, 86, 88, 95, 96, 116, 123
Aliphatic	Acetate	Unsaturated	B	1	7
Aliphatic	Acid	Saturated	C	2	2, 122
Aliphatic	Alcohol	Saturated	D	13	23, 61, 65, 70, 76, 81, 83, 89, 97, 107, 112, 114, 124
Aliphatic	Alcohol	Unsaturated	E	2	8, 39
Aliphatic	Aldehyde	Saturated	F	9	1, 29, 30, 64, 67, 85, 92, 121, 140
Aliphatic	Aldehyde	Unsaturated	G	2	5, 38
Aliphatic	Amine	Saturated	H	21	24, 25, 43, 46, 49, 51, 52, 53, 54, 55, 56, 62, 73, 78, 84, 90, 98, 117, 125, 136, 138
Aliphatic	Amine	Unsaturated	I	2	9, 44
Aliphatic	Ether	Saturated	J	1	13,127
Aliphatic	Ether	Unsaturated	K	2	12
Aliphatic	Halogenated	Unsaturated	L	5	6, 10, 11, 74, 135
Aliphatic	Hydrocarbon	Saturated	M	3	69, 110, 111
Aliphatic	Ketone	Saturated	N	15	3, 40, 45, 50, 71, 72, 99, 100, 102, 103, 104, 105, 113, 115, 139
Aliphatic	Ketone	Unsaturated	O	3	87, 94, 109
Aromatic	Aldehyde	Saturated	P	2	15, 68
Aromatic	Alkylbenzene	Halogenated	Q	9	16, 17, 18, 32, 33, 34, 35, 37, 48
Aromatic	Alkylbenzene	Saturated	R	11	14, 26, 27, 28, 63, 79, 91, 126, 130, 144, 145
Aromatic	Alkylbenzene	Unsaturated	S	4	57, 108, 129, 143
Aromatic	Benzene	Halogenated	T	3	19, 31, 47
Aromatic	Ketone	Saturated	U	1	4
Aliphatic	Isocyanate		V	3	75, 80, 106
Aromatic	Isocyanate		W	5	119, 131, 132, 133, 134
Other			X	14	20, 36, 41, 42, 60, 66, 93, 101, 118, 120, 128, 137, 141, 142
Total				145	

carboxaldehyde, and 3-pyridine carboxaldehyde. For these, a value for P^o could not be obtained or reliably estimated. However, from the results presented below, we will propose that allyl ether should be classified as *c* while the other two should be classified as *p*.

Groups of chemicals

The database was also divided by chemical groups and subgroups, as given in Table 2. Our second objective is to analyze the data not only on the basis of *p* or *c* but to identify particular chemical features related to these two classifications which can be used to establish whether or not a particular chemical or group has been previously shown to react toward a nucleophilic group. Thus, 24 chemical groups or subgroups were identified (A to X) in Table 2. The letters, A to X, were also used in Table 1 to identify the group or subgroup into which each chemical was placed.

Data analysis

Statistical analysis

Table 1 was imported into BMDP Diamond for Windows (BMDP Statistical Software, Los Angeles, Calif.). This computer software was used for rapid preliminary analysis of data sets (regressions and correlations) to indicate the best possibilities to explore using the groups and subgroups listed in Table 2. The same data were imported into Sigma Plot for Windows (Version 3.0) and Sigma Stat for Windows (Version 2.0, Jandel Scientific, San Rafael, Calif., USA) for all final statistical analysis and plots presented in this report. These were performed using a Pentium-Pro personal computer (Micron Electronic) operating under Windows NT (Version 3.51, Microsoft Corp.). For both multiple linear regression and linear regression analyses, the level of significance was set at $P < 0.05$ to accept an independent variable (i.e., physicochemical descriptors listed in Table 1) as appropriate to estimate log RD_{50}, as well as requiring an r^2 value > 0.5. The multiple linear regression equations for which a constant and the coefficients are presented in Table 3 are of the form: log RD_{50} (ppm) = constant $-$ $(a \times \pi_2^H) - (b \times \Sigma\alpha_2^H) - (c \times \log L$ (Oil) or $d \times L^{16})$. The linear regression equations for which the coefficients are presented in Table 3 are of the form: log RD_{50} (ppm) = constant $-$ $(a \times \log L$ (Oil)); log L (Oil) = constant $-$ $(a \times \log P^o)$; and log RD_{50} (ppm) = constant + $(a \times \log P^o)$. The linear regression plots presented in this report include the regression and 95% prediction interval (95% PI) curves.

Organic chemistry basic principles to contrast p vs c chemicals

The *p* and *c* chemicals listed in Table 1 are simple organic chemicals. Whether they are reactive (i.e., electrophilic) or not towards a nucleophilic group can be decided (but not always absolutely or quantitatively) by consulting standard organic chemistry textbooks (Roberts and Caserio 1965; McMurry 1995; Yurkanis-Bruice 1995). As summarized by Sykes (1995), there are three types of reactions for organic chemicals: substitutions, additions and elimination. Organic chemicals can be classified as three types of reagents: nucleophiles (electron-rich), electrophiles (electron-deficient), and radicals. There are two effects, electronic and steric, through which the behavior of a particular atom or group can be influenced by the rest of the molecule of which it is a constituent part. Finally, simple organic chemicals can be organized by functional groups, as given in Table 2, with all compounds containing a particular group expected to have some chemical behavior in common.

Table 3 Results of the multiple linear regression model for π_2^H and $\Sigma\alpha_2^H$ with L when using log L (Oil) or log L^{16} and results of the linear regression model for log L (Oil), and log L^{16} or log P^o to estimate log RD_{50} for *p*, *c*, and *c* + *p* chemicals. The regression coefficients obtained to quantify the contribution of each independent variable to estimate log RD_{50} are listed for both models. Also, the results of the linear regression model for log P^o to estimate log L (Oil) are similarly presented. (*Log L(Oil)* Solubility coefficient on olive oil, *log* P^o vapour pressure, RD_{50} sensory irritation potency, *n* Number of chemicals, *s* standard error of the estimate, r^2 coefficient of determination)

Equations to estimate log RD_{50} (ppm)	π_2^H	$\Sigma\alpha_2^H$	log L (Oil)	log L^{16}	log P^o	Constant	*s*	r^2	*n*	Type of chemicals from Table 1
Eq a	−0.711	−1.137	−0.861			6.777	0.342	0.85	58	*p*
Eq b			−0.855			6.250	0.407	0.78	58	*p*
Eq c	−1.437	−2.316		−0.774		7.049	0.354	0.84	58	*p*
Eq d				−0.633		5.503	0.564	0.60	58	*p*
Eq e			−0.226			2.777	0.855	0.06	61	*c*
Eq f				−0.171		2.607	0.859	0.04	62	*c*
Eq g					0.887	2.693	0.363	0.83	59	*p*
Eq h					0.422	1.288	0.932	0.23	83	*c*
Eq i					0.335	2.056	1.137	0.10	142	*p* + *c*
Equations to estimate log L (Oil)										
Eq j					−0.877	4.167	0.296	0.91	119	*p* + *c*
Eq k					−0.966	4.129	0.305	0.88	58	*p*
Eq l					−0.892	4.273	0.254	0.93	61	*c*

In toxicology, the limitation of the organic chemist's approach is that reactions are often described in environments far different than biological systems. This is where some difficulty may occur. Nevertheless, the above general rules are a good starting point as shown by Sexton (1963), Alarie (1973a,b), Hermens (1990a), Lipnick (1991), and Payne and Walsh (1994). We used this approach below to explain that the potency of *c* chemicals is higher than *p* chemicals on the basis of their electrophilic reactivity toward a nucleophilic group such as SH. Added to Syke's types of chemical reagents is a fourth category: nonreagents. These include chemicals such as the alkanes, alkylbenzenes, etc.; they are inert or nonreagent. Also, all nucleophiles in the database can be considered nonreagent; a nucleophile should not chemically react with the sensory irritant receptor which is expected to have nucleophilic centers, among other characteristics (Nielsen 1991).

Using these rules for nonreagents and nucleophiles in the database, we expect that stimulation of the sensory irritant receptor can be estimated from weak forces interactions only (i.e., physical mechanism) as previously described (Abraham et al. 1990; Alarie et al. 1995) and as shown in this report. In contrast, for the electrophiles in the database, we expect much higher potency. Finally, amines act as weak bases by accepting protons and thus are reactive chemicals capable of forming ionic bonds. We expect this series to be more potent than nonreactive chemicals as presented above (Nielsen and Vingaard 1988). Our analysis of *p* vs *c* chemicals given in the Discussion must then fit all these expectations. Table 4 was prepared to contrast the results between *p* vs *c* chemicals following these basic principles. Table 5 was also prepared, to investigate whether or not electronic and steric effects play a role in three different groups of *c* chemicals, again following these basic principles of organic chemistry.

Results

Selecting the most appropriate physicochemical descriptors to contrast *p* vs *c* chemicals

Multiple linear regression analysis: p vs c chemicals

The first series of analyses consisted of multiple linear regression analyses using the following independent variables listed in Table 1 to estimate log RD_{50}: R_2, π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ with one of the Ostwald partition coefficients, either log L (Oil) or log L^{16}. Some of the results are presented in Table 3. For *p* chemicals, R_2 and $\Sigma\beta_2^H$ were rejected as significant independent variables to estimate log RD_{50} and thus these results were excluded from Table 3. π_2^H and $\Sigma\alpha_2^H$, in combination with either log L (Oil) or log L^{16}, were accepted as significant to estimate log RD_{50} as shown by Eqs a and c given in Table 3. In contrast, for *c* chemicals, none of these independent variables were of significance to estimate log RD_{50} as shown by Eqs e and f in Table 3.

Linear regression analysis: p vs c chemicals

From the results of multiple linear regression analysis given above, L (Oil) and L^{16} were the most important descriptors to estimate log RD_{50} for *p* chemicals. Using these variables alone yielded Eqs b and d given in Table 3. Estimating log RD_{50} using only L (Oil) or L^{16} for *p* chemicals was satisfactory, with better results obtained with log L (Oil), (Eq b, $r^2 = 0.78$). Similar analysis with *c* chemicals yielded very poor estimating equations and the results were omitted from Table 3.

Using log P° instead of log L (Oil)

Log P^o was previously shown to be as good a descriptor as log L (Oil) to estimate log RD_{50} for *p* chemicals (Alarie et al. 1995). This is also clear from Table 3 (Eq g vs Eq b). For reactive chemicals, it sometimes becomes impossible to obtain L (Oil) values since they react with the solvent (e.g., isocyanates). And as shown in Table 1, values for log L (Oil) are missing for several moderately or highly reactive chemicals. Therefore, in order to contrast *p* vs *c* chemicals, it was deemed acceptable

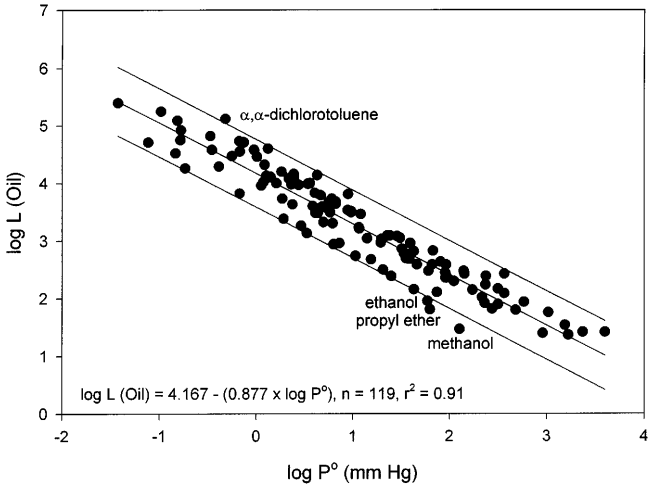

Fig. 1 Linear least squares regression analysis results for log P^o vs log L (Oil) for *p* and *c* chemicals listed in Table 1. The regression and 95% prediction interval (PI) curves are presented and the outliers are identified. (*Log* P^o Vapour pressure, *log L* (*Oil*) solubility coefficient on olive oil)

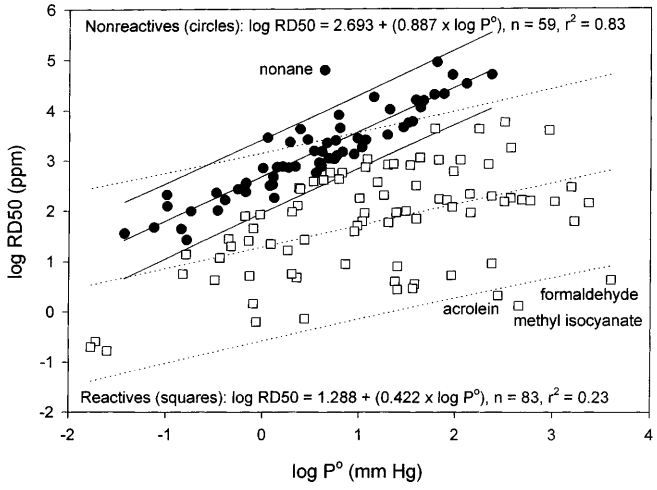

Fig. 2 Linear least squares regression analysis results for log P^o vs log RD_{50} for *p* (nonreactives; *circles*) and *c* (reactives; *squares*) chemicals listed in Table 1. The regression and 95% PI curves are presented and the outliers are identified. (RD_{50} Sensory irritation potency)

to use log P^o instead of log L (Oil). It is also important to use log P^o in order to evaluate Ferguson's proposed rule as described above. Only three values are missing for log P^o in Table 1. A linear regression analysis of log P^o vs log L (Oil) was conducted in order to verify that log P^o can be substituted for log L (Oil). The results are presented in Table 3 and Fig. 1, indicating that log P^o can be substituted for log L (Oil) for *p*, *c*, and *p* + *c* chemicals Eqs (j), (k), (l). With such results presented in Table 3 and Fig. 1, we substituted log P^o for log L (Oil) as a measure of lipophilicity, to contrast *p* vs *c* chemicals and to simultaneously evaluate Ferguson's rule.

Contrasting *p* vs *c* chemicals

Using log P^o *to contrast p vs c chemicals*

Figure 2 presents the results of linear regression analysis of log P^o vs log RD_{50} for *p* and *c* chemicals listed in Table 1. For *p* chemicals, log P^o is an excellent descriptor to estimate log RD_{50}, while it is a very poor descriptor to estimate log RD_{50} for *c* chemicals: $r^2 = 0.83$ for *p*, $r^2 = 0.23$ for *c*.

Analysis of groups and subgroups of chemicals using log P^o

Nonreactive alkylbenzenes vs related reactive chemicals

Several groups and subgroups of *c* chemicals can be compared to one group of *p* chemicals as presented in Fig. 3. For the alkylbenzenes, there is an excellent correlation between log P^o and log RD_{50}. The chlorinated alkylbenzenes (2-chlorotoluene, 2-chloroethylbenzene, and α,α-dichlorotoluene) were more potent than the alkylbenzenes. Similarly, the chlorobenzyl chlorides and halogenated benzyls were more potent. Their potency is in the order of the reactivity of their halogen leaving group toward a nucleophilic group. Thus, *o-* > *p-* > *m-*chlorobenzylchloride and I > Br > benzylchloride (Roberts and Caserio 1965). Still more potent were the isocyanates, the most potent being the diisocyanates. The high reactivity of mono- and di- isocyanates towards nucleophiles in biological systems is well-known (Brown et al. 1987).

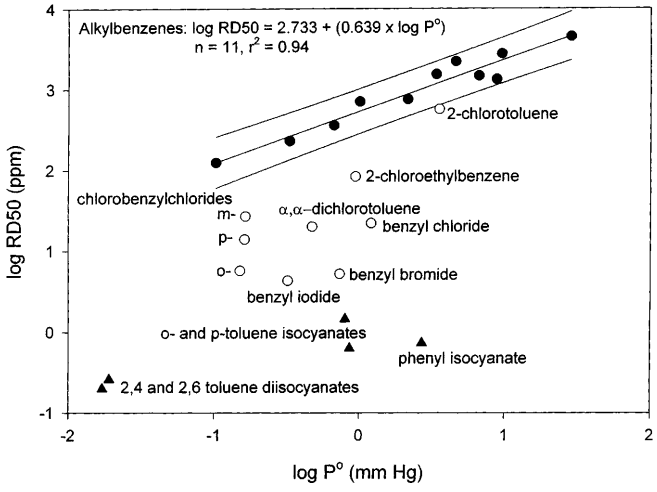

Fig. 3 Linear least squares regression analysis results for log P^o vs log RD_{50} for alkylbenzenes (*closed circles*); the regression and 95% PI curves are presented. Related *c* chemicals (halogenated alkylbenzenes, *open circles*) and aromatic isocyanates (*triangles*) are also shown for comparison

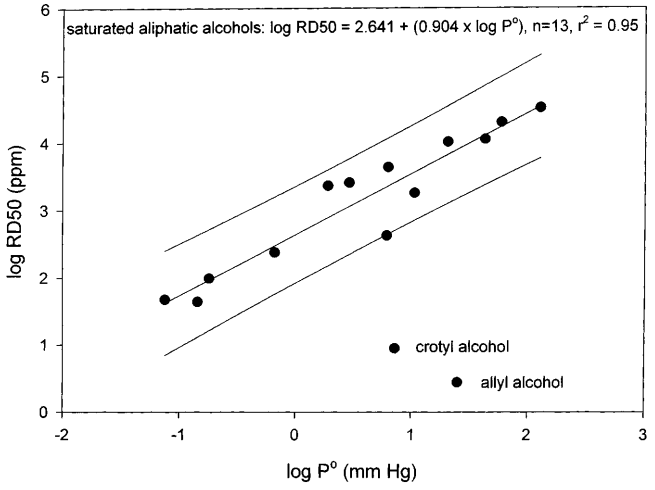

Fig. 4 Linear least squares regression analysis results for log P^o vs log RD_{50} for saturated aliphatic alcohols; the regression and 95% PI curves are presented. The results for corresponding unsaturated alcohols are also shown

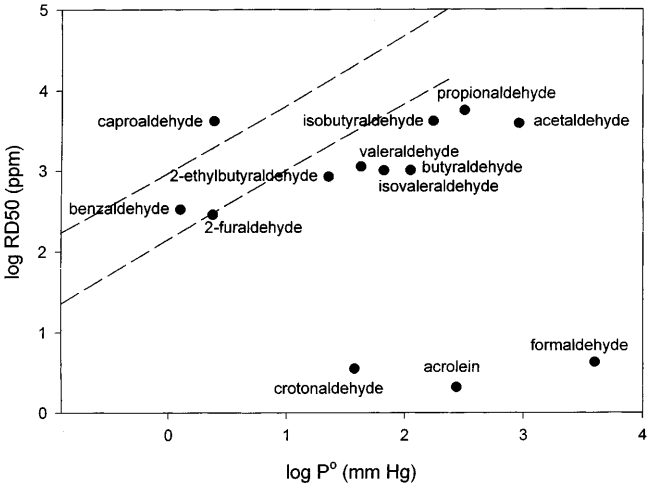

Fig. 6 Scatter plot of the results of log P^o vs log RD_{50} for aldehydes. The 95% PI curves (*dashed lines*) obtained for saturated ketones (from Fig. 5) are shown for comparison

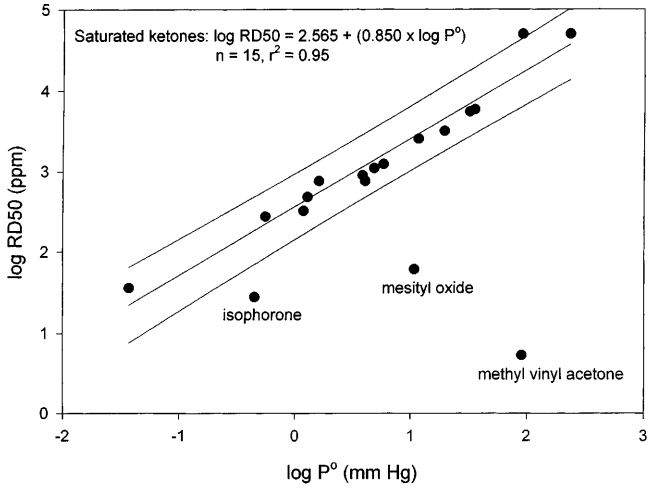

Fig. 5 Linear least squares regression analysis results for log P^o vs log RD_{50} for saturated ketones; the regression and 95% PI curves are presented. The results for corresponding unsaturated ketones are also shown

Alcohols and ketones

Figure 4 presents the results for alcohols. The unsaturated crotyl and allyl alcohols were much more potent than predicted by the series of saturated alcohols ($n = 13$) for which the regression curve is presented. Fig. 5 presents the results for ketones. The same pattern observed with alcohols was also found with the ketones. Unsaturation is responsible for their reactivity towards nucleophilic groups as discussed below.

Aldehydes, amines, and acetates

Figure 6 presents the results for aliphatic aldehydes ($n = 11$) with the 95% PI curves obtained for saturated ketones ($n = 15$) for comparison. No relationship between log P^o and log RD_{50} was found for saturated aliphatic aldehydes ($n = 9$). As found for the alcohols and ketones, the unsaturated aldehydes were much more potent than the saturated aldehydes and this is also true for formaldehyde. All saturated aliphatic aldehydes have a $P^{RD50}/P^o < 0.1$, (i.e., *c* chemicals) with the exception of caproaldehyde, and indeed no relationship should be found. Their potencies (i.e., RD_{50} values) are within one log unit of one another while their log P^o values vary over 3.5 log units. The aromatic aldehydes, benzaldehyde, and 2-furaldehyde, are within the 95% CI of *p* chemicals as illustrated in Fig. 6. As for the alcohols and ketones, unsaturation in aliphatic aldehydes is responsible for their high reactivity towards nucleophilic groups and the high reactivity of formaldehyde towards such groups is well-established (Yurkanis-Bruice 1995). The results presented in Fig. 7 for the amines are the same as those obtained with the aldehydes. All amines have a $P^{RD50}/P^o < 0.1$ (i.e., *c* chemicals) and no relationship should be found between log P^o and log RD_{50}. Again, the unsaturated amines are more potent, as found for alcohols, ketones, and aldehydes. The results presented in Fig. 8 show that the acetates ($n = 13$) have the same degree of potency regardless of their log P^o values, except when the carbon is secondary or tertiary as shown by isopropyl and tert-butyl acetates. These are less potent. It has been suggested previously (Kamlet et al. 1987) that the short chain acetates with a primary carbon to the oxygen may hydrolyze to acetic acid which would be the active species. It has also been demonstrated that esters are hydrolyzed in the nasal mucosa via carboxylesterases (Bogdanffy et al. 1987). The result for acetic acid is shown and it is in this potency range. As for the homologous series presented above, the unsaturated allyl acetate was much more potent than the 12 saturated acetates. The higher potency of these three groups and subgroups will be discussed below.

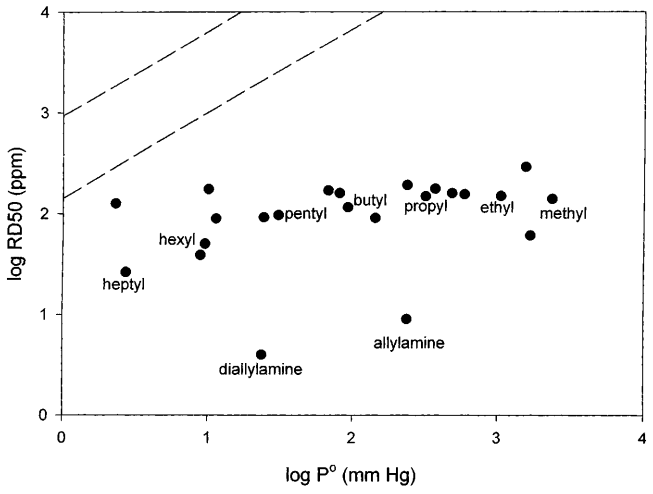

Fig. 7 Scatter plot of the results of log P^o vs log RD_{50} for amines. The saturated primary aliphatic amines and unsaturated amines are identified. The 95% PI curves (*dashed lines*) obtained for saturated ketones (from Fig. 5) are shown for comparison

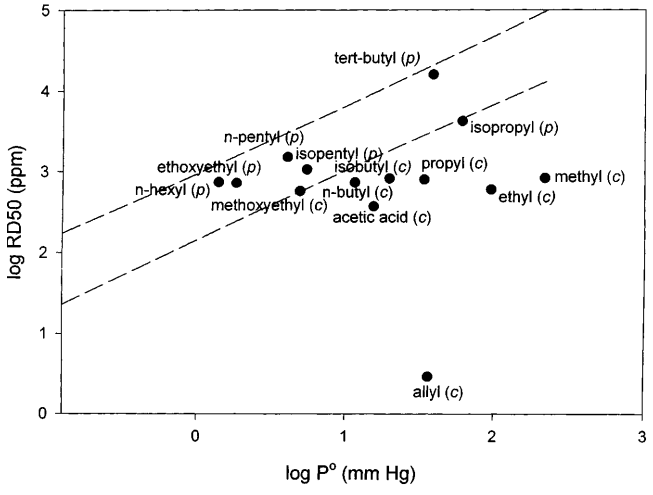

Fig. 8 Scatter plot of the results of log P^o vs log RD_{50} for aliphatic acetates. The secondary and tertiary acetates and unsaturated acetate are identified. Acetic acid and the 95% PI (*dashed lines*) curves obtained for saturated ketones (from Fig. 5) are shown for comparison

Discussion

Comparing various nonreactive-reactive pairs: replacing the empirical P^{RD50}/P^o ratio of Ferguson

Table 4 presents a variety of pairs of chemicals to contrast *p* vs *c* chemicals. It was organized to separate five different mechanisms of chemical reactivity, I to V, as listed in Table 4. For each mechanism, the pairs were sorted for excess potency due to chemical reactivity. To arrive at this excess potency, we first calculated the RD_{50} ratio for each pair (ratio A in Table 4). To correct for changes in P^o due to a different chemical group in each pair, we next calculated the P^o ratio for each pair (ratio B in Table 4). Our estimate of excess potency, due to chemical reactivity, was calculated as ratio A/ratio B, as is also listed in Table 4.

For mechanism I (nucleophilic substitution reaction of halogen group), the RD_{50} ratios of the pairs varied from 11 to 1052. The substitution with halogens had a significant lowering effect on P^o (and as expected, the opposite effect on lipophilicity). This was corrected by taking into account their P^o ratio (2.4–88; Table 4). With this correction (A/B), the range is now 1.6 to 129. The chemicals are in the correct order of increasing chemical reactivity from their chemical structure. The negligible increase with chlorobenzene or bromobenzene was expected since these halogens attached directly to an aromatic ring are not good leaving groups (Yurkanis-Bruice 1995). If there is separation by one CH_2, as in benzyl chloride, iodide, or bromide, the increase in excess potency is because such groups will increase the positive charge on the α carbon, increasing its nucleophilic reactivity (Yurkanis-Bruice 1995). Finally for mechanism I, *o*-chlorobenzyl chloride showed the highest excess potency. The added ring chloride will further add to the α carbon positive charge. This influence decreased as the addition was made in the meta or para position, thus lowering the potency (see Fig. 5) as expected (Roberts and Caserio 1965).

For mechanism II (addition to C=C, influenced by neighboring groups), the range of RD_{50} ratios is very wide, starting at 4.8 for ethylbenzene/styrene to 17 800 for propyl ether/allyl ether. The effect of unsaturation on P^o or L (Oil) was much smaller for this series, except for the ethers. When correcting for this effect, the range became 3.4 to 9507. The lowest excess potency was for ethylbenzene vs styrene. This is expected since there is no electron withdrawing group present to activate the α carbon to promote nucleophilic addition. The fact that the range for the increase in potency is so large is consistent with the fact that nucleophilic addition at the α carbon of the double bond is greatly influenced by the nature of neighboring groups, such as electron withdrawing groups as well as their distance from the double bond. Furthermore, steric hindrance must also be taken into account. These are well-known rules in organic chemistry (Roberts and Caserio 1965; Charton 1973; McMurry 1995; Yurkanis-Bruice 1995) and have been shown to be applicable to the sensory irritation receptor when evaluating a homologous series of similar reactive chemicals evaluated as aerosols instead of vapors (Alarie 1973a, b; Tarantino and Sass 1974). If glutathione is taken as a representative nucleophile, the reaction with the unsaturated chemicals listed is well-documented (Arias and Jacoby 1976; Friedman 1973). However, we cannot find from the literature reactivity descriptors to explain the effect of each type of neighboring group to the C=C group.

The role of chemical reactivity for this series can be investigated further by inspecting the data of Table 5. Pairs of unsaturated aldehydes, alcohols, and ketones are presented along with their saturated homologues

Table 4 Related pairs of chemicals: effect of chemical reactivity

Pair no.	Chemical	Ratio A RD_{50} Ratio of each pair (1st/2nd)	Ratio B P^o Ratio of each pair (1st/2nd)	Ratio A/B Excess potency due to chemical reactivity	Chemical reactivity mechanism[a]
1	Toluene (*p*)				
	Bromobenzene (*c*)	11	6.8	1.6	I
2	Toluene (*p*)				
	Chlorobenzene (*c*)	4.3	2.4	1.8	I
3	Toluene (*p*)				
	Benzylchloride (*c*)	205	23	9	I
4	Toluene (*p*)				
	Benzyl iodide (*c*)	1052	88	12	I
5	Toluene (*p*)				
	Benzyl bromide (*c*)	870	38	23	I
6	*p*-Xylene (*p*)				
	o-Chlorobenzyl chloride (*c*)	232	58	129	I
7	Ethylbenzene (*p*)				
	Styrene (*c*)	4.8	1.4	3.4	II
8	Propyl amine (*c*)				
	Allyl amine (*c*)	17	1.3	13	II
9	Dipropyl amine (*c*)				
	Diallyl amine (*c*)	23	1.0	23	II
10	4-Methyl pentane-2-one (*p*)				
	Mesityl oxide (*c*)	52	1.8	29	II
11	Propyl alcohol (*p*)				
	Allyl chloride (*c*)	6.0	0.1	60	II[c]
12	Butyraldehyde (*c*)				
	Crotonaldehyde (*c*)	287	3.0	96	II
13	Propyl acetate (*c*)				
	Allyl acetate (*c*)	273	1.0	273	II
14	Propyl alcohol (*p*)				
	Allyl iodide (*c*)	150	0.5	300	II
15	Propyl alcohol (*p*)				
	Allyl bromide (*c*)	48	0.1	480	II
16	Propyl ether (*p*)				
	Allyl glycidyl ether (*c*)	15 614	31	505	II
17	Butyl alcohol (*p*)				
	Crotyl alcohol (*c*)	491	0.9	545	II
18	Propyl ether (*p*)				
	Allyl ether (*c*)	17 800	31[b]	576	II
20	Proprionaldehyde (*c*)				
	Acrolein (*c*)	2751	1.2	2293	II
21	Propyl alcohol (*p*)				
	Allyl alcohol (*c*)	3775	0.8	4718	II
22	Methyl ethyl ketone (*p*)				
	Methyl vinyl ketone (*c*)	9507	1.0	9507	II
23	Methanol (*p*)				
	Formaldehyde (*c*)	7851	0.032	245 343	III
24	Ethanol (*p*)				
	Acetaldehyde (*c*)	5.3	0.060	88	III
25	Propan-1-ol (*o*)				
	Propionaldehyde (*c*)	1.8	0.064	28	III
26	Butan-1-ol (*p*)				
	Butyraldehyde (*c*)	4.3	0.056	76	III
27	Pentan-1-ol (*p*)				
	Valeraldehyde (*c*)	2.0	0.044	45	III
28	Toluene				
	Benzaldehyde	13.5	2.9	4.7	III
28	Methanol (*p*)				
	Methylamine (*c*)	236	0.048	4916	IV
29	Ethanol (*c*)				
	Ethylamine (*c*)	135	0.056	2410	IV
30	Propan-1-ol (*p*)				
	Propylamine (*p*)	69.4	0.064	1084	IV
31	Butan-1-ol (*p*)				
	n-Butylamine (*c*)	37.6	0.068	553	IV
32	Pentan-1-ol (*p*)				
	Pentylamine (*c*)	23.9	0.060	398	IV

(continued overleaf)

Table 4 (continued)

Pair no.	Chemical	Ratio A RD_{50} Ratio of each pair (1st/2nd)	Ratio B P^o Ratio of each pair (1st/2nd)	Ratio A/B Excess potency due to chemical reactivity	Chemical reactivity mechanism[a]
33	*n*-Hexanol (*p*)				
	Hexylamine (*c*)	4.7	0.070	67	IV
34	*n*-Heptanol (*p*)				
	Heptylamine (*c*)	3.7	0.070	52	IV
35	Methanol (*p*)				
	Methyl isocyanate (*c*)	25 668	0.280	91 671	V
36	*n*-Hexanol (*p*)				
	Hexyl isocyanate (*c*)	49.8	0.290	171	V
37	Ethyl benzene (*p*)				
	Phenyl isocyanate (*c*)	3761	3.5	1074	V
38	Toluene (*p*)				
	Phenyl isocyanate (*c*)	6197	11	564	V
39	*p*-Xylene (*c*)				
	p-Toluene isocyanate (*c*)	2103	11	191	V
40	*o*-Xylene (*p*)				
	2,4-Toluene diisocyanate (*p*)	7335	389	19	V

[a] I, Nucleophilic substitution reaction of halogen group; II, addition to C=C, influenced by neighboring groups; III, addition to C=O of aldehydes; IV, reaction of amines, primary *n*-alkylamines only; V, addition to N=C=O group of isocyanates
[b] vapor pressure is not available, made equal to allyl glycidyl ether
[c] Pairs 11, 14, and 15 can also be under mechanism I (Nielsen and Bakbo 1985); Eder et al. (1980)

used to calculate excess potency. Large differences were observed in excess potency between the unsaturated pairs in each chemical group. This cannot be explained by the difference in P^o or inappropriate pairing with the saturated homologues (Nielsen et al. 1984). Rather, this large difference is attributable to the small structural change between the unsaturated pairs. As shown in Table 5, the largest excess potency in these unsaturated pairs of chemicals is when the structure is $H_2C=CH-R$, regardless of R containing an aldehyde, alcohol, or ketone group. With the change to $(CH_3)CH=CH-R$ for the aldehyde and alcohol, the excess potency was lower. It was further reduced with the change to $(CH_3)_2C=CH-R$ for the ketone. CH_3 or $(CH_3)_2$ exerted a great influence, as expected, on how nucleophilic attack can occur at the α carbon of C=C (Roberts and Caserio 1965, Yurkanis-Bruice 1995).

These examples clearly show that unsaturation itself is far from a good guide to estimate possible excess potency, even when electron withdrawing groups are present. Steric hindrance and electronic effects exerted by the CH_3 group must be considered. Our results can be compared to those obtained by McCarthy et al. (1994) who measured the reactivity with glutathione of several acrylate esters at pH 7.4 under the same conditions. The difference between methyl acrylate and methyl methacrylate was a factor of 160. This difference was also attributed to the electronic and steric influence of the CH_3 group on the α carbon. The closest comparison with our data set is between mesityl oxide and methyl vinyl ke-

Table 5 Effects of electron withdrawing groups and electronic and steric effects of substituents at C=C

Pairs	Chemical	Formula	RD_{50} (ppm)	P^o (mm Hg)	Excess potency[a]
Aldehydes					
Unsaturated	Crotonaldehyde	$CH_3CH=CHCHO$	3.53	38	96
	Acrolein	$H_2C=CHCHO$	2.07	275	2293
Saturated	Butyraldehyde	$CH_3CH_2CH_2CHO$	1015	110	–
	Proprionaldehyde	CH_3CH_2CHO	5695	317	–
Alcohols					
Unsaturated	Crotyl alcohol	$CH_3CH=CHCH_2OH$	8.70	7	505
	Allyl alcohol	$H_2C=CHCH_2OH$	2.75	25	4718
Saturated	Butyl alcohol	$CH_3CH_2CH_2CH_2OH$	4375	6	–
	Propyl alcohol	$CH_3CH_2CH_2OH$	10381	21	–
Ketones					
Unsaturated	Mesityl oxide	$(CH_3)_2C=CHCOCH_3$	61.1	11	29
	Methyl vinyl ketone	$H_2C=CHCOCH_3$	5.3	90	9507
Saturated	4-Methylpentan-2-one	$(CH_3)_2CHCH_2COCH_3$	3195	20	–
	Butan-2-one	$CH_3CH_2COCH_3$	50196	91	–

[a] From Table 4

tone, as given in Table 5. We found a factor of 300 for this pair.

The role of chemical reactivity as given in Table 4 is further elucidated with the unsaturated amines. Allyl and diallyl amines were much more potent than the saturated amines. These unsaturated amines, enamines, also promote nucleophilic addition at the α carbon (McMurry 1995) and their higher potency is expected from the same reactivity mechanism.

For mechanism III (nucleophilic addition to the carbonyl group of aldehydes), we observed a large excess potency with the first pair of the series, methanol vs formaldehyde (A/B = 245 343). This difference abruptly decreased with decreasing log P^o as the number of methylene groups increased. Again the high reactivity of formaldehyde toward nucleophilic groups is well-documented as is the reactivity of other aldehydes toward such groups (Roberts and Caserio 1965). No quantitative reactivity descriptors toward glutathione could be found to explain the difference between formaldehyde and acetaldehyde and the following members in this series. However, the reaction of formaldehyde with water as the nucleophile is well-documented and again the CH_3 group in acetaldehyde exerts great steric and electronic influence, decreasing this reaction (McMurry 1995; Yurkanis-Bruice 1995). The same rule applies to explain the nonreactivity of the C=O group of the saturated ketones.

For mechanism IV (reaction of amines, primary *n*-alkyl amines), the chemical reactivity of the listed saturated amines should be the same since they have similar pKa values (Nielsen and Vinggard 1988; Nielsen and Yamagiwa 1989). If their $P^{RD\,50}/P^o$ is plotted vs the number of CH_2 groups, as shown in Fig. 9, we observed a linear increase in this ratio since their RD_{50} values are approximately the same, while their P^o is linearly decreasing. This gives the impression that chemical reactivity is increasing with increasing chain length.

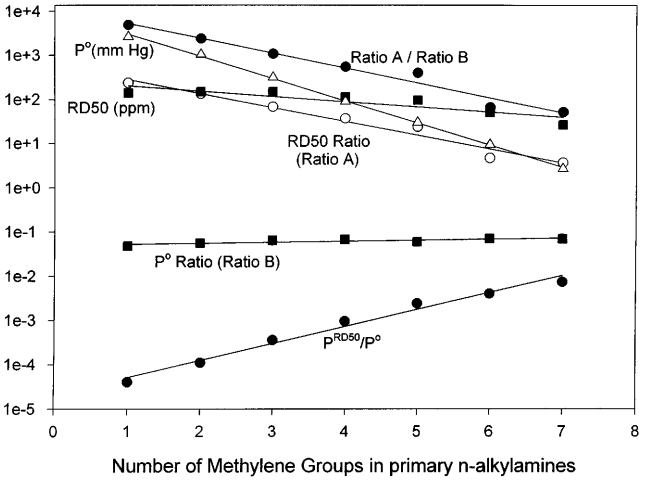

Fig. 9 Linear least squares regression analysis results for primary *n*-alkylamines by plotting various results given in Tables 1 and 4 vs the number of CH_2 groups for each amine

However, this is not so. When plotting the alcohol/amine ratio for RD_{50} (ratio A in Table 4) and for P^o (ratio B in Table 4), we obtained almost constant values for ratio B but linearly declining values for ratio A. Comparing the plot of ratio A/ratio B (i.e., excess potency due to chemical reactivity) with the plot of ratio A, we obtained a constant decline for both with increasing chain length. Furthermore, a constant separation of 1.3 log unit or a factor of 20 is present between the two curves. Thus, for this series, the chemical reactivity descriptor must be constant (and it should be so according to the pKa) for all members and this factor of 20 is a true measure of chemical reactivity in the biological system investigated. Steric influence was not present, and the simple addition of CH_2 groups was taken into account by the P^o correction. For mechanism V, the reactivity of isocyanates toward nucleophiles under biological conditions is well-established (Brown et al. 1987).

Other nonreactive-reactive databases

We have reviewed three comprehensive sources of quantitative structure-activity relationships (QSAR) data (Karcher and Devillers 1990; Wermuth 1993; Hansch and Leo 1995) as well as a computerized database (Medline) to find other examples of reactive-nonreactive databases. None exists in inhalation toxicology except for 89 volatile organic chemicals evaluated for their potency to induce narcosis in mice (Filov et al. 1979). These researchers used Ferguson's rule to separate *p* vs *c* chemicals as done in Table 1, but made no attempt to explain their findings. However, there are some relevant examples in aquatic toxicology, where researchers obtained good QSAR equations for homologous series of nonreactive chemicals using lipophilicity as a descriptor of acute toxic effects and pointed out a few outliers having higher than predicted toxicity. In such cases, the authors also concluded that the higher than predicted toxicity was due to chemical reactivity towards a nucleophilic group, as reviewed by Hermens (1990a,b), Lipnick (1991), Hansch and Leo (1995), and Cronin and Dearden (1995).

Evaluating our findings

Figure 10 presents the data for 11 chemicals which we classified as 'others' in Table 2 and identified with the letter X in Table 1 when originally formulating this database. It can be seen that all X chemicals classified as *p* in Table 1 are in this category as shown in Fig. 10, when using the saturated ketones as the standard for *p* chemicals. The saturated ketones group was used for comparison because it has the widest range of log P^o values and the narrowest 95% PI of the *p* homologous series: alcohols, alkylbenzenes, ketones. Ethyl acrylate and methyl crotonate are aliphatics with unsaturated

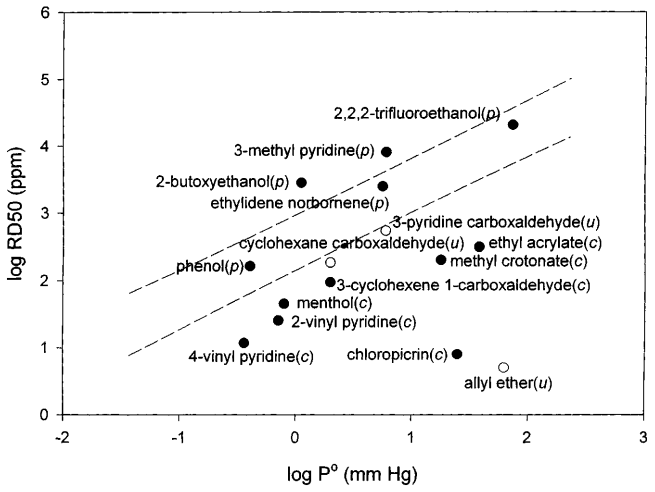

Fig. 10 Scatter plot for the chemicals classified as 'others' (letter X in Table 1, *closed circles*). The *p* or *c* classification, as listed in Table 1, is shown in *parenthesis*. The 95% PI curves (*dashed lines*) obtained for saturated ketones are shown for comparison. Also, three chemicals classified as *u* in Table 1 are shown (*open circles*) using the log P^o value of propyl ether for allyl ether, 3-cyclohexene 1-carboxaldehyde for cyclohexane carboxaldehyde, and 3-methyl pyridine for 3-pyridine carboxaldehyde

double bonds and with neighboring electron withdrawing groups which should follow the same rule of being reactive toward a nucleophile as presented above for unsaturated alcohols, aldehydes, and ketones and also as noted above from the results obtained by McCarty et al. (1994). Thus, they should be classified as *c* chemicals as shown in Fig. 10. The same is true for 2 and 4-vinyl pyridine, which are aromatics with an unsaturated double bond side-chain activated by the nitrogen in the pyridine ring. The reactivity of chloropicrin toward a nucleophile is obvious and this chemical properly falls in the *c* category in Fig. 10. The exception is menthol. It was classified as *c* in Table 1 and should be, in our opinion, a *p* chemical. It is slightly more potent than predicted as a *p* chemical as shown in Fig. 10 but there is no obvious reason. We cannot find from the literature that this chemical would react with a nucleophile. However, its deviation from a *p* chemical is not large. This misclassification is probably due to an error in the P^o value for menthol (0.8 mm Hg) listed in Schaper (1993). Based upon data in CRC Handbook of Chemistry and Physics (1991), a better estimate would be 0.1–0.2 mm Hg. Hence, menthol would be classified as *p* and would no longer be an exception. Thus, this set of chemicals further helps us in verifying our proposal. Three chemicals are listed as unclassified (*u*) in Table 1, as explained in the Materials and methods, because no log P^o could be obtained or reliably estimated. They have been added to Fig. 10 (open circles) using the saturated homologue log P^oor a closely related chemical as given in Fig. 10. When doing so, it can be seen in Fig. 10 that these three were properly classified as *p* or *c* chemicals on the basis of chemical structures as presented above.

Relevant descriptors for reactivity

The evidence presented in this report supports the existence of both physical and chemical mechanisms for the activation of the sensory irritant receptor. While physical descriptors can be used to estimate the potency of nonreactive chemicals as shown in this report as well as previously (Abraham et al. 1990, 1994; Alarie et al. 1995, 1996), no chemical reactivity descriptor can be proposed at this time. An empirical factor of 20 was found for the primary *n*-alkylamines and can serve as a starting point to obtain a mechanistic descriptor. Furthermore, the data for the many other related amines offers the opportunity to explore steric hindrance and differences between primary, secondary, and tertiary amines. If chemical reactivity descriptors can be arrived at for each group and subgroup, there is then a possibility to combine them with a lipophilicity descriptor (or substituting vapor pressure for highly reactive chemicals) to arrive at an estimating equation. For example, Verhaar et al. (1993) explored this possibility for S_N2 reactivity using computational chemistry, as well as using measured reactivity descriptors for nucleophilic addition under a given set of conditions. While no firm conclusion was arrived at because of a limited data set, the much more extensive data sets presented here provide the opportunity to explore this approach further. Similarly, Veith and Mekenyan (1993) and Schultz et al. (1995) have proposed some descriptors of electrophilicity, which in conjunction with a lipophilicity descriptor helped explain excess potency in aquatic toxicology. Another example is presented by Roberts (1995) for skin sensitization of a series of chemicals according to their electrophilic reactivity. Chemical reactivity, however, may not be the only explanation. With more complex structures, stereoelectronic criteria must be taken into account. This has been demonstrated with other series of sensory irritants evaluated as aerosols: capsaicin congeners, 4-cyclohexylmethylcyclohexylamine derivatives, and a series of diimines (Alarie 1990).

Conclusions

We have assembled the largest database of reactive-nonreactive volatile organic chemicals available in toxicology. These chemicals induced the same effect: sensory irritation. We conclude that Ferguson's proposition is correct that both physical (for nonreactive) or chemical (for reactive) mechanisms can result in the same toxicological effect. Our results strongly suggest that relevant descriptors for chemical reactivity would be appropriate to estimate the potency of reactive volatile organic chemicals as sensory irritants. Before such information is obtained, a semi-quantitative estimate of potency for an untested volatile organic reactive chemical can be arrived at by comparison with the many reactive chemicals in the database. Estimating the potency of nonreactive chemicals from physicochemical des-

criptors as originally suggested by Abraham et al. (1990) is further validated.

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