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Physicochemical Properties of Nonreactive Volatile Organic Chemicals to Estimate RD50: Alternatives to Animal Studies

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This article presents the correlations obtained between the results on the potency of nonreactive airborne chemicals as sensory irritants and several of their physicochemical properties. The potency of airborne sensory irritants obtained from a reflexively induced decrease in respiratory frequency has been measured in the past using mice. Typically, their potency has been expressed as the exposure concentration necessary to decrease respiratory frequency by 50% (RD50). A large database of RD50 values is now available and such values are highly correlated with occupational exposure guidelines such as threshold limit values (TLVs). We used the nonreactive volatile organic chemicals from this database, for which relevant physicochemical variables are available or can be calculated. These variables were vapor pressure (P) or Ostwald gas–liquid partition coefficients (L). The liquids used for L values were *n*-hexadecane, octanol, *N*-formylmorpholine, tri-(2-ethylhexyl)phosphate, and olive oil. Excellent correlations were found between log RD50 and log P, as well as between log RD50 and log L^{16}, log L(Oct), log L(NFM), log L(EHP), or log L(Oil). It follows that as an alternative to the bioassay, these physicochemical variables can be used to estimate RD50 of nonreactive volatile organic chemicals. Appropriate exceptions to general estimation of RD50 values from physicochemical variables are also presented, as well as the most appropriate estimates which can be obtained within homologous series.

In 1966, Alarie proposed the use of breathing pattern modifications in unanesthetized mice to evaluate the potency of airborne chemicals as sensory irritants. The bioassay relied upon measuring a decrease in respiratory frequency occurring reflexively from stimulation of trigeminal nerve endings in the nasal mucosa. Typically, the potency of airborne sensory irritants has been expressed as the concentration necessary to decrease respiratory frequency by 50% (RD50). In 1982, Nielsen and Alarie proposed that for nonreactive chemicals, such as alkylbenzenes and alcohols, the mechanism for stimulation of trigeminal nerve endings would be via physical interaction, rather than chemical interaction with a receptor protein. This conclusion was arrived at from the fact that the ratio "RD50 vapor pressure/saturated vapor pressure," was approximately constant for these chemicals. This followed the suggestion of Ferguson (1939). Thus, RD50 values could be estimated from vapor pressure, at least for nonreactive chemicals (Alarie and Luo, 1986). Muller and Greff (1984) and Roberts (1986) also attempted to estimate RD50 using physicochemical properties of nonreactive chemicals such as boiling point and molecular weight. In 1990, Abraham *et al.* presented a linear multiple regression equation using the following physicochemical variables to estimate RD50: (a) solute dipolarity, (b) solute hydrogen—bond acidity, (c) solute hydrogen—bond basicity, (d) a polarizability correction term, (e) solute volume, and (f) the solute Ostwald solubility coefficient (L) (gas–liquid partition coefficient) on *n*-hexadecane (L^{16}) at 298K. With these descriptors, a much better estimation of RD50 values was obtained. Of the above descriptors in the regression equation, L^{16}, a measure of the lipophilicity of a solute, was the major contributor in estimating RD50 values. Abraham (1995) has recently updated the results using a larger number of nonreactive chemicals, again with excellent results. This is not unexpected. Indeed, lipophilicity has been shown to be a requirement for a wide variety of toxic or pharmacologic effects (Dearden, 1985; Leo, 1985). For sensory irritants, the solute dipolarity and hydrogen-bond acidity of the physicochemical properties noted above are also significant descriptors in the multiple linear regression analysis. Therefore the receptor characteristic for nonreactive volatile organic chemicals for sensory irritation can be described as moderately dipolar, quite basic, and highly lipophilic (Abraham, 1995). Furthermore, it has also been shown that RD50 values can be estimated from Ostwald solubility coefficients (L) for nonreactive volatile organic chemicals, when using wet octanol (Oct), *N*-formylmorpholine (NFM) or tri-(2-ethylhexyl)phosphate (EHP), but not water, as the solvents. With these solvents, a formal irritant–receptor interac-

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tion mechanism was proposed, these solvents being in fact good models for the receptor site for nonreactive sensory irritants (Abraham *et al.*, 1994b). Thus, more than an empirical correlation (estimation) was obtained.

Since values for vapor pressure (P), L^{16}, L(Oct), L(NFM), and L(HEP) as well as values for olive oil, L(Oil) are available or can be measured and the data base of RD50 values for nonreactive chemicals is now quite large (Schaper, 1993), we have studied the possibility of estimating RD50 values from these physicochemical variables. What is particularly attractive is the fact that L^{16} values for nonaromatic chemicals, at least, can now be obtained from calculations, as shown by Havelec and Sevcick (1994).

In this article we present the results for physicochemical variables which can be used for estimating RD50 values. With this approach we propose that the bioassay can be eliminated when nonreactive volatile organic chemicals need to be evaluated, provided that some precautions are taken when making those estimations.

MATERIALS AND METHODS

RD50 Values

We used the data base of Schaper (1993) to prepare the list of chemicals presented in Table 1. We selected only nonreactive (or chemicals of low reactivity) volatile organic chemicals for which values for all of the physicochemical variables listed below were available or could be calculated. From this data base we identified 58 chemicals with RD50 values obtained in Swiss–Webster, OF1 or CF1 male mice. For five chemicals, two RD50 values were available for the same strain, we used the average value. For 14 chemicals, RD50 values were available for two of the above strains and for two chemicals RD50 values were available for all three strains. This yielded a total of 74 entries in Table 1. We added the recent results for 2,2,2-trifluoroethanol (G. D. Nielsen, unpublished data), for a total of 59 chemicals and 75 entries in Table 1.

Physicochemical Variables

Vapor pressures for the chemicals listed in Table 1 are given as log P, with P in mm Hg.

The Ostwald solubility coefficients (L), equivalent to gas–solvent partition coefficients are defined as,

$$L = \frac{\text{concentration of solute in solvent}}{\text{concentration of solute in the gas phase}}.$$

Both concentrations are expressed in the same units, e.g., mol/liter, and therefore L values listed in Table 1 are dimensionless.

Experimental values in olive oil at 37°C are from Abraham *et al.* (1987), those in *N*-formylmorpholine at 40°C are from Weidlich *et al.* (1987), and those in tri-(2-ethylhexyl) phosphate at 37°C are from Alessi *et al.* (1978). Values in hexadecane at 25°C, denoted as L^{16}, are from Abraham *et al.* (1987) and Abraham (1993). The L values in octanol at 25°C were obtained by combining L values in water from Abraham *et al.* (1994a) with water–octanol partition coefficients, Leo (1994).

Values of log L in Table 1 marked as "calculated" were obtained through equations of the type shown as Eq. (1) using the equation coefficients given by Abraham (1995)

$$\log \text{SP} = c + r \cdot R_2 + s \cdot \pi_2^{\text{H}} + a \cdot \sum \alpha_2^{\text{H}} + b \cdot \sum \beta_2^{\text{H}} + l \cdot \log L^{16}. \quad (1)$$

The descriptors used in Eq. (1) are set out as follows in Abraham (1993):

R_2, an excess molar refraction that can be determined simply from a knowledge of the compound refractive index, Abraham (1993), Abraham *et al.* (1990a,b).

π_2^{H}, the solute dipolarity/polarizability, it being not possible to devise descriptors for these properties separately.

$\Sigma\alpha_2^{\text{H}}$, the solute overall or effective hydrogen-bond acidity.

$\Sigma\beta_2^{\text{H}}$, the solute overall or effective hydrogen-bond basicity.

log L^{16}, the solute Ostwald partition coefficient on hexadecane at 25°C (Abraham *et al.*, 1987).

The descriptors are combined into a general linear equation, as previously described by Abraham (1993), where log SP in Eq. (1) is a property for a series of solutes in a given system. Thus SP can be L, the Ostwald solubility coefficient for a number of solutes in a particular organic solvent. Then if SP is known for a series of solutes for which descriptors are available, Eq. (1) can be solved by the method of multiple linear regression analysis, to yield the constants c, r, s, a, b, and l. Not every descriptor in Eq. (1) may be significant; a descriptor is retained only if its contribution is statistically significant ($p < 0.05$).

Statistical Analysis

Single physicochemical property analysis. The values for RD50 and the physicochemical variables of Table 1 were entered into Sigma Stat for Windows (Jandel Scientific, San Rafael, CA) for linear least-squares regression analysis including calculation of 95% confidence interval (95% CI) for the regression line and 95% prediction interval (95% PI) for an individual value. The results were then entered into Sigma Plot for Windows (Jandel Scientific) to plot the individual data points, the regression and 95% PI curves (Figs. 1–6). A sufficient number of entries for three homologous series, alcohols, alkylbenzenes, and ketones, was also found from Table 1 for regression analysis. The plots are presented in the same manner (Figs. 7–9).

Multiple physicochemical properties analysis. Using Eq. (1) we can substitute log SP with log RD50 values listed in Table 1 and solve the equation using the physicochemical descriptors values (Abraham *et al.*, 1994a,b) for each chemical. This was conducted using either log L^{16} or log L(Oil) values in Eq. (1). These analyses were conducted using Sigma Stat for Windows with the multiple linear regression analysis option.

RESULTS

Single Physicochemical Variables

Results of the regression analyses for the data in Table 1 are presented in Figs. 1 to 6 and are self explanatory.

For three homologous series of chemicals in Table 1, the same statistical analyses were conducted with the results presented in Figs. 7 to 9. For these, we present the regression analysis only with log P or log L(Oil) since these are the two physicochemical properties which can best estimate log RD50 values. For the alkylbenzenes (Fig. 7) the series is from toluene to *n*-hexylbenzene and includes the unsaturated styrene and divinylbenzene. For the alcohols (Fig. 8) the series is from methanol to octanol but does not include butoxyethanol or 2,2,2-trifluoroethanol. The latter would be

TABLE 1

Values for RD50 and for the Following Physicochemical Variables: log *L* Tri-2-ethylhexyl) Phosphate (EHP) at 37°C; log *L* Wet Octanol (Oct) at 25°C; log *L* *N*-Formylmorpholine (NFM) at 40°C; log *L* *n*-Hexadecane (L^{16}) at 25°C; log *L* Olive Oil (Oil) at 37°C; log Vapor Pressure (*P*) at 25°C

Chemical	CAS No.	log *L* (EHP)	log *L* (Oct)	log *L* (NFM)	log L^{16}	log *L* (Oil)	log *P* (mm Hg)	log RD50 (ppm)
Acetophenone	98-86-2	4.60[a]	4.94	5.01[c]	4.50	4.58[a]	−0.430	2.01
Benzaldehyde	100-52-7	4.15[c]	4.43	4.64[c]	4.00	4.13[c]	0.117	2.52
Bromobenzene	108-86-1	3.94	4.06	3.99[c]	4.04	4.14	0.622	2.61
Butan-1-ol	71-36-3	3.78	4.34	3.70[c]	2.60	2.94	0.832	3.10
Butan-1-ol	71-36-3	3.78	4.34	3.70[c]	2.60	2.94	0.832	3.77
Butan-2-one	78-93-3	2.49	3.01	2.65	2.28	2.36	1.957	4.03
Butan-2-one	78-93-3	2.49	3.01	2.65	2.28	2.36	1.957	3.95
Butan-2-one	78-93-3	2.49	3.01	2.65	2.28	2.36	1.957	4.50
2-Butoxyethanol	111-76-2	4.70[c]	5.42	4.45[c]	3.80	3.95[c]	0.045	3.45
n-Butylbenzene	104-51-8	4.43[c]	4.67	3.92[c]	4.73	4.46	0.036	2.85
t-Butylbenzene	98-06-6	4.59[c]	4.43	3.65[c]	4.41	4.17[c]	0.345	2.88
4-*t*-Butyltoluene	98-51-1	5.29[c]	4.66[c]	4.03[c]	4.92	4.55[c]	−0.173	2.56
Chlorobenzene	108-90-7	3.56	3.71	3.53[c]	3.65	3.46	1.082	3.02
2-Chloroethylbenzene	622-24-2	4.60[c]	4.76[c]	4.81[c]	4.60	4.58[c]	−0.030	1.92
2-Chlorotoluene	95-49-8	4.01	4.26	3.89[c]	4.17	4.00[c]	0.550	2.76
Cyclohexanone	108-94-1	3.92	4.41	4.14[c]	3.79	3.83[c]	0.609	2.88
1,2-Dichlorobenzene	95-50-1	4.41	4.43	4.45[c]	4.51	4.60	0.144	2.26
3,3-Dimethylbutan-2-one	75-97-8	3.01	3.48	2.94[c]	2.92	2.86[c]	1.505	3.75
2,6-Dimethylheptan-4-one	108-83-8	4.17	4.57[c]	3.80[c]	4.24	4.02[c]	0.235	2.51
1,4-Divinylbenzene	1321-74-0	4.68	4.86[c]	4.64[c]	4.90	4.73[c]	−0.219	1.89
Ethanol	64-17-5	2.82	3.37	2.86	1.48	1.96	1.771	4.13
Ethanol	64-17-5	2.82	3.37	2.86	1.48	1.96	1.771	4.44
2-Ethoxyethylacetate	111-15-9	3.91[c]	4.75[c]	4.00[c]	3.74	3.75[c]	0.401	2.86
Ethylbenzene	100-41-4	3.58	3.73	3.25	3.77	3.49	0.978	3.16
Ethylbenzene	100-41-4	3.58	3.73	3.25	3.77	3.49	0.978	3.61
2-Ethylhexan-1-ol	104-76-7	5.40	5.84[c]	4.89[c]	4.43	4.52[c]	−0.844	1.64
Furfural	98-01-1	3.68[c]	4.11[c]	4.62[c]	3.26	3.63[c]	0.197	2.46
n-Heptane	142-82-5	2.73[c]	2.54	1.58	3.17	2.59	1.660	4.19
Heptan-1-ol	111-70-6	5.14	5.81	4.74[c]	4.11	4.26	−0.630	1.99
Heptan-2-one	110-43-0	3.80	4.21	3.66[c]	3.76	3.60	0.584	2.95
Heptan-4-one	123-19-3	3.74	4.18	3.58[c]	3.70	3.59[c]	0.681	3.04
Hexan-1-ol	111-27-3	4.69	5.26	4.39[c]	3.61	3.82	−0.143	2.38
Hexan-2-one	591-78-6	3.35	3.79	3.32[c]	3.26	3.21	1.065	3.41
n-Hexyl acetate	142-92-7	4.27[c]	4.49	3.87[c]	4.35	4.11[c]	0.146	2.87
n-Hexylbenzene	1077-16-3	5.30[c]	5.55	4.58[c]	5.72	5.25[c]	−0.978	2.10
Isoamyl acetate	123-92-2	3.70[c]	3.79	3.38[c]	3.74	3.55[c]	0.737	3.02
Isopropylbenzene	98-82-8	3.84[c]	3.88	3.43	4.08	3.79	0.668	3.29
Isopropylbenzene	98-82-8	3.84[c]	3.88	3.43	4.08	3.79	0.668	3.40
Methanol	67-56-1	2.51	3.00	2.72	0.97	1.47	2.104	4.62
Methanol	67-56-1	2.51	3.00	2.72	0.97	1.47	2.104	4.40
2-Methoxyethylacetate	110-49-6	3.52[c]	4.39[c]	3.79[c]	3.29	3.38[c]	0.642	2.76
3-Methylbutan-1-ol	123-51-3	4.14	4.40	3.90[c]	3.01	3.17	0.459	3.65
3-Methylbutan-1-ol	123-51-3	4.14	4.40	3.90[c]	3.01	3.17	0.459	2.86
5-Methylheptan-3-one	541-85-5	4.15	4.56[c]	3.85[c]	4.20	4.00[c]	0.201	2.88
5-Methylhexan-2-one	110-12-3	3.63	4.07[c]	3.48[c]	3.60	3.49[c]	0.761	3.09
4-Methylpentan-2-ol	108-11-2	4.10	4.52	3.71[c]	3.17	3.30[c]	0.787	2.63
4-Methylpentan-2-one	108-10-1	3.18	3.55	3.12[c]	3.08	2.97	1.288	3.50
2-Methylpropan-1-ol	78-83-1	3.60	4.06	3.49[c]	2.41	2.74	1.059	3.26
α-Methylstyrene	98-83-9	4.09	4.26	3.95[c]	4.29	4.10[c]	0.386	2.44
Nonan-5-one	502-56-7	4.62	4.82	4.26[c]	4.69	4.47[c]	−0.258	2.44
n-Octane	111-65-9	3.18[c]	3.04	1.94	3.67	3.04	1.147	4.26
Octan-1-ol	111-87-5	5.58	6.07	5.09[c]	4.61	4.71	−1.090	1.67
Octan-2-one	111-13-7	4.24	4.48	4.01[c]	4.25	4.09[c]	0.013	2.68
Pentan-1-ol	71-41-0	4.24	4.91	4.05[c]	3.10	3.38	0.336	3.61
Pentan-1-ol	71-41-0	4.24	4.91	4.05[c]	3.10	3.38	0.336	2.78
Pentan-2-one	107-87-9	2.90	3.49	2.92	2.75	2.70	1.549	3.77

TABLE 1—*Continued*

Chemical	CAS No.	log L (EHP)	log L (Oct)	log L (NFM)	log L^{16}	log L (Oil)	log P (mm Hg)	log RD50 (ppm)
n-Pentyl acetate	628-63-7	3.82[c]	4.14	3.52[c]	3.84	3.48	0.613	3.17
n-Pentyl acetate	628-63-7	3.82[c]	4.14	3.52[c]	3.84	3.48	0.613	3.19
n-Pentylbenzene	538-68-1	4.88[c]	5.07	4.27[c]	5.23	4.82[c]	−0.484	2.36
Propan-1-ol	71-23-8	3.32	3.81	3.23	2.03	2.50	1.303	3.68
Propan-1-ol	71-23-8	3.32	3.81	3.23	2.03	2.50	1.303	4.10
Propan-1-ol	71-23-8	3.32	3.81	3.23	2.03	2.50	1.303	4.14
Propan-2-ol	67-63-0	2.86	3.53	2.90	1.76	2.16	1.637	3.70
Propan-2-ol	67-63-0	2.86	3.53	2.90	1.76	2.16	1.637	4.25
Propanone	67-64-1	2.10	2.55	2.36	1.69	1.92	2.364	4.89
Propanone	67-64-1	2.10	2.55	2.36	1.69	1.92	2.364	4.37
n-Propylbenzene	103-65-1	3.98[c]	4.11	3.55[c]	4.23	3.99	0.536	3.18
Styrene	100-42-5	3.72	3.86	3.67[c]	3.85	3.68	0.782	2.77
Styrene	100-42-5	3.72	3.86	3.67[c]	3.85	3.68	0.782	2.75
Toluene	108-88-3	3.18	3.38	2.93	3.32	3.08	1.454	3.53
Toluene	108-88-3	3.18	3.38	2.93	3.32	3.08	1.454	3.71
2,2,2-Trifluoroethanol	75-89-8	3.44[c]	3.60[c]	3.98[c]	1.22	2.11[c]	1.869	4.32
Undecan-2-one	112-12-9	5.55	5.67	5.03[c]	5.73	5.40[c]	−1.194	1.56
o-Xylene	95-47-6	3.75	3.78	3.44	3.93	3.64	0.825	3.17
p-Xylene	106-42-3	3.64	3.74	3.23	3.83	3.53	0.945	3.12

Note. The following is a list of calculated values which could be used for some of the chemicals, instead of using their measured values. 2-Chlorotoluene: log L (oct) = 3.95; 1,2-dichlorobenzene: log L (oil) = 4.41; 4-methylpentan-2-ol: log L (oct) = 4.70; nonan-5-one: log L (oct) = 5.00; *n*-pentyl acetate: log L (oil) = 3.66; undecan-2-one: log L (oct) = 5.89. The L^{16} value listed for 1,4-divinylbenzene is an estimated value. c, calculated values.

included within the 95% PI range while the former would fall just outside the higher 95% PI curve. For the ketones (Fig. 9), the series is from propanone to undecan-2-one. It does include cyclohexanone but not acetophenone. The value for this last chemical is within the 95% PI range.

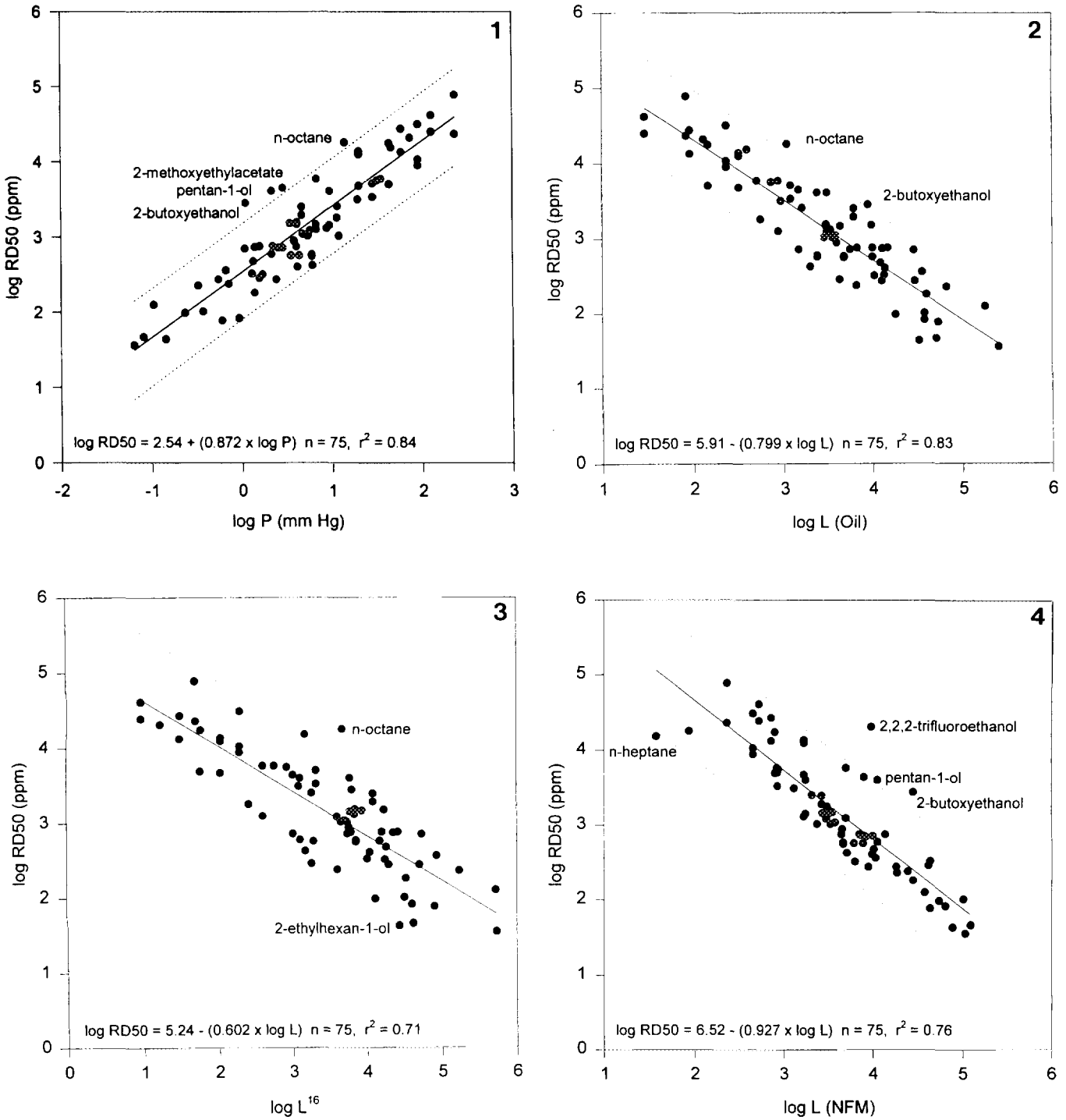
Multiple Physicochemical Variables

The results of the multiple linear regression analysis using L^{16} or L(Oil) in Eq. (1) indicated that only π_2^H and $\Sigma\alpha_2^H$ made a significant additional contribution to using L values alone. However, this contribution was small with L(Oil). Using only log L(Oil) to estimate log RD50 (Fig. 2) yielded an r^2 value of 0.83, adding the two above descriptors raised this value to 0.88. With L^{16}, the contribution of the above two descriptors was larger, raising r^2 from 0.71 with log L^{16} alone (Fig. 3) to 0.88. The multiple linear regression equations are: log RD50 (ppm) = $6.66 - (0.776 \times \pi_2^H) - (1.15 \times \Sigma\alpha_2^H) - (0.85 \times \log L(\text{Oil}))$ and log RD50 (ppm) = $6.90 - (1.49 \times \pi_2^H) - (2.37 \times \Sigma\alpha_2^H) - (0.761 \times \log L^{16})$.

DISCUSSION

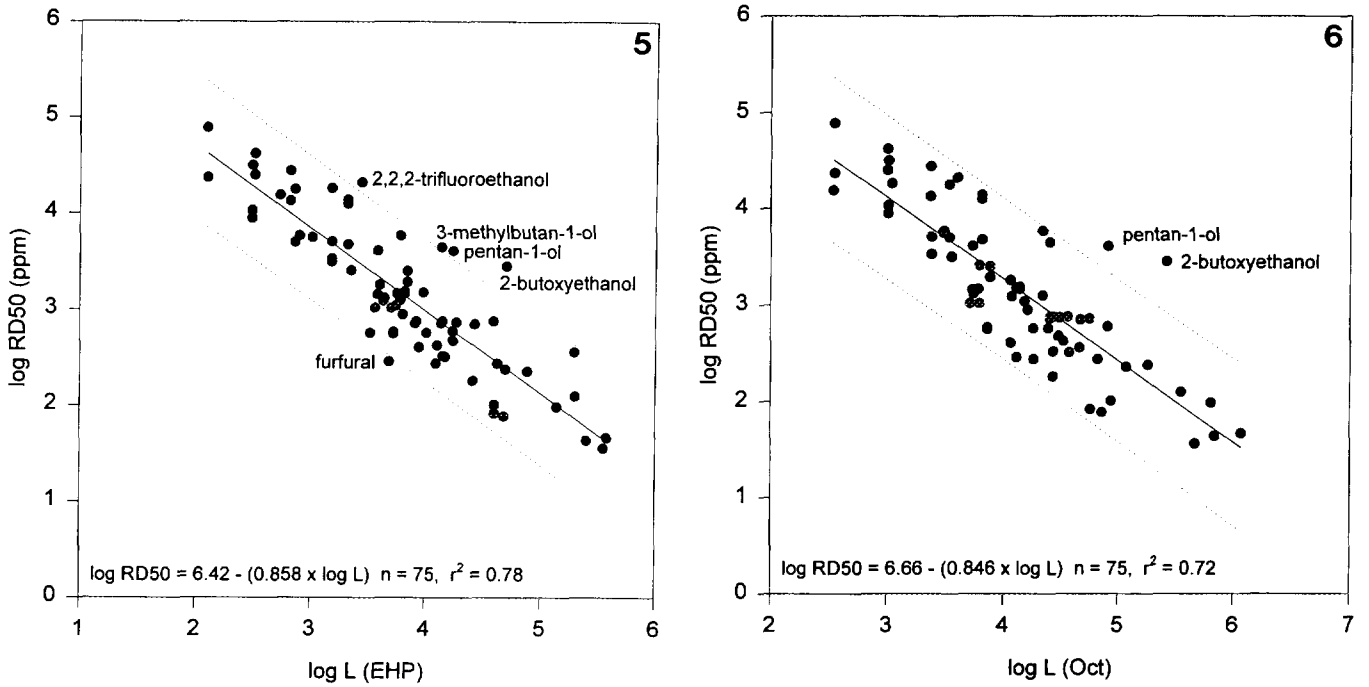
The results show that for a wide variety of nonreactive organic volatile chemicals, as listed in Table 1, there is an excellent correlation between the log RD50 values obtained in mice and log L values using a variety of solvents. Also there is an excellent correlation between log RD50 values and log P. Particularly impressive correlations were obtained between log RD50 and log L(Oil) or log RD50 and log P. Thus estimating RD50 from these physicochemical properties is an appropriate alternative to animal studies when new nonreactive volatile organic chemicals need to be investigated. Adding other physicochemical descriptors to log L(Oil) did not materially improve the estimation of RD50; therefore, log L(Oil) values alone can be used.

The following reservations should be kept in mind when estimating RD50 from the physicochemical variables presented. Some nonreactive chemicals are likely to be much more potent than predicted. These should be few. As listed in the data base compiled by Schaper (1993), capsaicin or *cis*-4-cyclohexylmethylcyclohexylamine and their congeners (Alarie 1990) are nonreactive chemicals but will activate the sensory irritant receptor in a much more specific manner than the nonreactive volatile organic chemicals listed in Table 1 (Nielsen 1991). These were solids, evaluated as aerosols rather than vapors. Some nonreactive volatile organic chemicals are also likely to be inactive as sensory irritants. Again, these should be few. One example can be given. For benzene, from log P, the RD50 would be estimated to be 18,880 ppm. Benzene is inactive as a sensory irritant. Concentrations above 2000 ppm induce clear acute systemic toxicity, interfering with measurement of the trigeminal reflex for eval-



FIGS. 1–6. Linear least-squares regression curves with 95% PI for each physicochemical variable listed in Table 1 vs log RD50 values. Data points falling outside the 95% PI are identified.

uating sensory irritation (Nielsen and Alarie, 1982). This may occur with other chemicals inducing anesthesia rapidly, preventing the reflex sensory irritation reaction to be measured. Thus it is desirable to use the bioassay to verify that the calculated RD50 value for a new nonreactive volatile organic is indeed a good estimate. This can be verified with



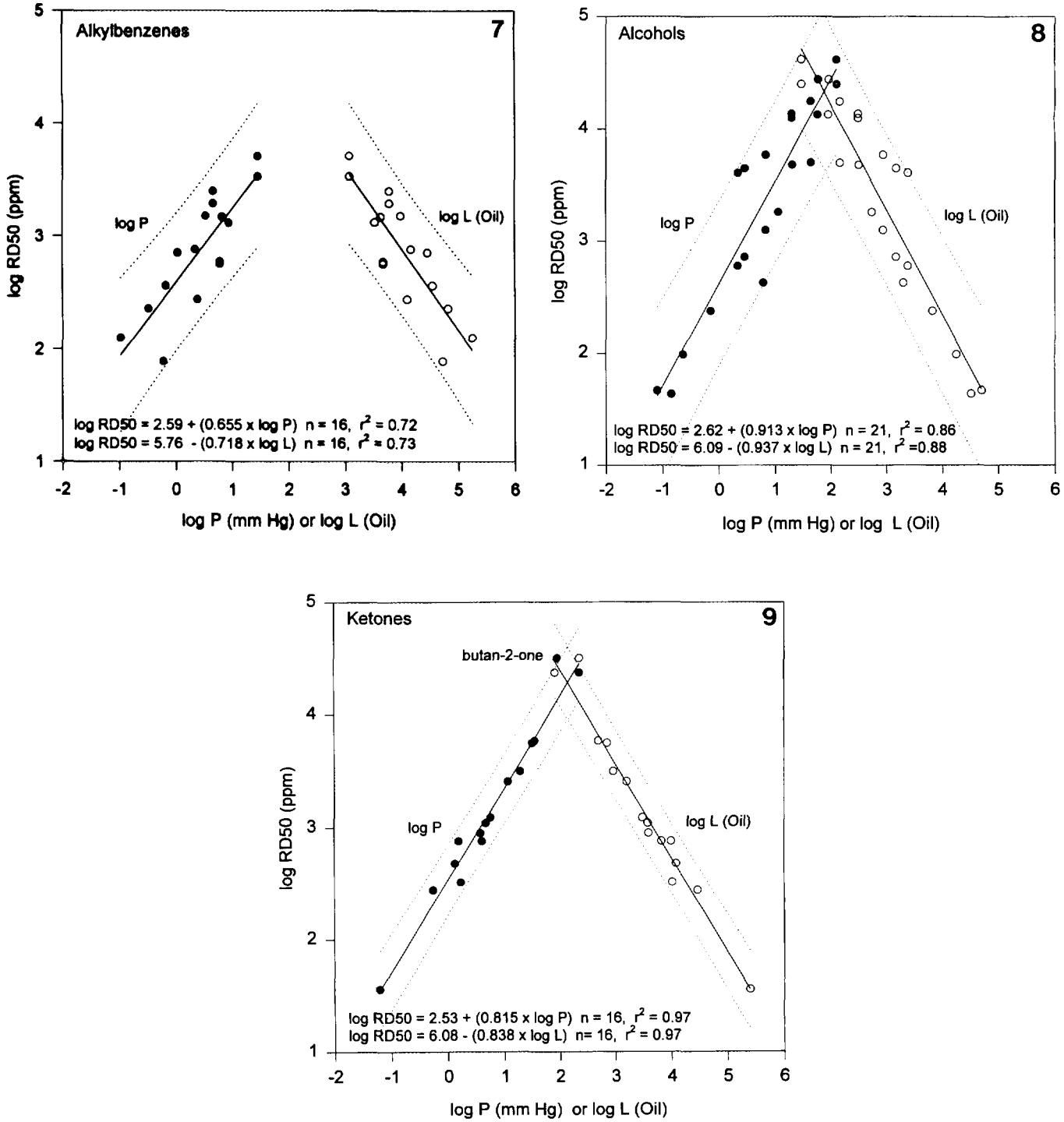
FIGS. 1–6—*Continued*

exposure of a single group of four animals at the estimated RD50 concentration, or alternatively two groups, one on each side of the estimated RD50.

We have previously discussed the fact that within a series of homologous chemicals, their potency increases with decreasing vapor pressure or increasing lipophilicity (Figs. 7–9) (as for the general case, Figs. 1–6), as the number of carbons in the chain increases (Abraham *et al.*, 1994). Within each homologous series, there will be a cutoff point as the receptor pocket, which behaves as a solvent for these nonreactive volatile organic chemicals, becomes too small to accommodate the larger chemicals in the series (Abraham *et al.*, 1994b). The cutoff point is a well-known phenomenon (Ferguson, 1939; Franks and Lieb, 1982, 1990). This restricts the use of physicochemical variables to estimate RD50 for new chemicals with longer chain length than those evaluated. Again, the estimated RD50 value should be verified using one group of four animals. The safest use of these physicochemical properties to estimate RD50 is within homologous series, when interpolating within the lowest and highest members evaluated, as shown in Figs. 7–9. In these cases, there is no reason to use the bioassay at all.

We noted the outliers found in the analysis of the data sets. It would be worthwhile to have as large a data set with RD50 values on a single strain and from a single laboratory instead of with three strains of mice and from multiple laboratories. This would most probably reduce the variation. However, it is unlikely to produce very different regression equations. We have tested this possibility with the results for alkylbenzenes and alcohols obtained in Swiss–Webster mice reported by Nielsen and Alarie (1982) by combining these two homologous series for regression of log P vs RD50 values. The regression equation for the combined homologous series (n = 15) is: log RD50 = 2.48 + (0.886 × log P) and the results are presented in Fig. 10. This is not different than for the entire data set (Fig. 1), but r^2 increased from 0.83 to 0.93 and the 95% PI is narrower. This comparison is not entirely fair, since the sets are not equal in either the number or variety of chemicals. However, while it did indicate a reduced variation, as expected, the prediction equation was not modified which is the most important aspect.

In conclusion, the results presented indicate that the bioassay can be either eliminated or greatly reduced in the number of animals needed, when RD50 values for nonreactive chemicals are required such as when threshold limit values for exposure guidelines are to be obtained, as described by Schaper (1993). Recently, Cometto-Muniz and Cain (1994) have further substantiated that the potency of sensory irritants in mice is well correlated with their potency in humans, thus further enhancing the calibrated aspect of this bioassay (Schaper, 1993). It follows that estimating RD50 for mice will also estimate potency for humans.



FIGS. 7–9. Linear least-squares regression curves with 95% PI for log P (mm Hg) or log L(Oil) values vs log RD50 values listed in Table 1 for three homologous series: alkylbenzenes (Fig. 7), alcohols (Fig. 8), and ketones (Fig. 9).

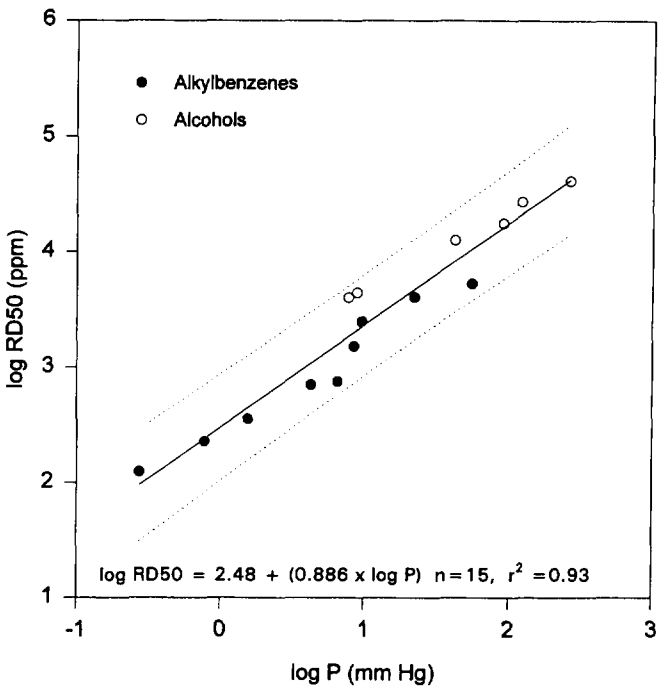


FIG. 10. Linear least-squares regression curve with 95% PI for log P (mm Hg) values vs log RD50 values for alcohols and alkylbenzenes results reported by Nielsen and Alarie (1982).

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REFERENCES

Abraham, M. H. (1993). Scales of solute hydrogen-bonding: Their construction and application to physicochemical and biochemical processes. *Chem. Soc. Rev.* **22,** 73–83.

Abraham, M. H. (1995). The potency of gases and vapors: QSARs—anesthesia, sensory irritation and odor. In *Indoor Air and Human Health Revisited: Bringing Selected Advances in Medical Science to the Indoor Air Quality Community* (D. Gammage, Ed.), Lewis, Chelsea, MI, in press.

Abraham, M. H., Grellier, P. L., and McGill, R. A. (1987). Determination of olive oil–gas and hexadecane–gas partition coefficients, and calculation of the corresponding olive oil–water and hexadecane–water partition coefficients. *J. Chem. Soc. Perkin Trans.* **2,** 797–803.

Abraham, M. H., Andonian-Haftvan, J., Whiting, G. S., Leo, L., and Taft, R. W. (1994a). Hydrogen bonding. 34. The factors that influence the solubility of gases and vapours in water at 98K, and a new method for its determination. *J. Chem. Soc. Perkin Trans.* **2,** 1777–1791.

Abraham, M. H., Nielsen, G. D., and Alarie, Y. (1994b). The Ferguson principle and an analysis of biological activity of gases and vapors. *J. Pharm. Sci.* **83,** 680–688.

Abraham, M. H., Whiting, G. S., Alarie, Y., Morris, J. J., Taylor, P. J., Doherty, R. M., Taft, R. W., and Nielsen, G. D. (1990a). Hydrogen Bonding. 12. A new QSAR for upper respiratory tract irritation by airborne chemicals in mice. *Quant. Struct.-Act. Relat.* **9,** 6–10.

Abraham, M. H., Whiting, G. S., Doherty, R. M., and Shuely, W. J. (1990b). Hydrogen bonding. 13. A new method for the characterization of GLC stationary phases—The Laffort data set. *J. Chem. Soc. Perkin Trans.* **2,** 1451–1460.

Alarie, Y. (1966). Irritating properties of airborne materials to the upper respiratory tract. *Arch. Environ. Health* **13,** 433–449.

Alarie, Y. (1990). Trigeminal nerve stimulation: Practical Application for Industrial Workers and Consumers. In *Chemical Senses:* Irritation (B. G. Green, J. R. Mason, and M. R. Kare, Eds.), Vol. 2, pp. 297–304. Dekker, New York.

Alarie, Y., and Luo, J. E. (1986). Sensory irritation by airborne chemicals: A basis to establish acceptable levels of exposure. In *Toxicology of the Nasal Passages* (C. S. Barrow, Ed.), pp. 91–100. Hemisphere, New York.

Alessi, P., Kikic, I., Papo, A., and Torriano, G. (1978). Gas chromatographic characterization of phosphate esters. *J. Chem. Eng. Data* **23,** 29–33.

Cometto-Muniz, J. E., and Cain, W. S. (1994). Sensory reactions of nasal pungency and odor to volatile organic compounds: The alkylbenzenes. *Am. Ind. Hyg. Assoc. J.* **55,** 811–817.

Dearden, J. C. (1985). Partitioning and lipophilicity in quantitative structure–activity relationships. *Environ. Health Perspect.* **61,** 203–228.

Ferguson, J. (1939). The use of chemical potentials as indices of toxicity. *Proc. R. Soc. London Ser. B* **127,** 387–404.

Franks, N. P., and Lieb, W. R. (1982). Molecular mechanisms of general anesthesia. *Nature* **300,** 487–493.

Franks, N. P., and Lieb, W. R. (1990). Mechanisms of anesthesia. *Environ. Health Perspect.* **87,** 199–205.

Havelec, P., and Sevcick, J. G. K. (1994). Concept of additivity for a non-polar solute–solvent criterion log L^{16}. Nonaromatic compounds. *J. Chromatogr. A* **677,** 319–329.

Leo, A. (1985). Parameter and structure–activity data bases: Management for maximum utility. *Environ. Health Perspect.* **61,** 275–286.

Leo, A. (1994). *The Pomona MedChem Data Project.* Claremont, CA.

Muller, J., and Greff, G. (1984). Recherche de relations entre toxicite de molecules d'interet industrial et proprietes physicochimiques: Test d'irritation des voies aeriennes superieures applique a quatre familles chimiques. *Food Chem. Toxicol.* **22,** 661–664.

Nielsen, G. D. (1991). Mechanisms of activation of the sensory irritant receptor by airborne chemicals. *CRC Crit. Rev. Toxicol.* **21,** 183–208.

Nielsen, G. D., and Alarie, Y. (1982). Sensory irritation, pulmonary irritation and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe exposure levels and correlation with their thermodynamic properties. *Toxicol. Appl. Pharmacol.* **65,** 459–477.

Roberts, D. W. (1986). QSAR for upper-respiratory tract irritation. *Chem.-Biol. Interact.* **57,** 325–345.

Schaper, M. (1993). Development of a database for sensory irritants and its use in establishing occupational exposure limits. *Am. Ind. Hyg. Assoc. J.* **54,** 488–544.

Weidlich, U., Rohm, H.-J., and Gmehling, J. (1987). Measurement of γ^{∞} using GLC.2: Results for the stationary phases *N*-formylmorpholine and *N*-methylpyrrolidone. *J. Chem. Eng. Data* **32,** 450–453.