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Supplemental Material
https://escholarship.org/uc/item/6mn862w6#supplemental

Data Availability
The data associated with this publication are in the supplemental files.

Peer reviewed

The Biological and Toxicological Activity of Gases and Vapors

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Abstract − A large amount of data on the biological and toxicological activity of gases
and vapors has been collected from the literature. Processes include sensory irritation
thresholds, the Alarie mouse test, inhalation anesthesia, etc. It is shown that a single
equation using only five descriptors (properties of the gases and vapors) plus a set of
indicator variables for the given processes can correlate 643 biological and non-lethal
toxicological activities of 'non-reactive' compounds with a standard deviation of 0.36 log
unit. The equation is scaled to sensory irritation thresholds obtained by the procedure of
Cometto-Muñiz, and Cain, and provides a general equation for the prediction of sensory
irritation thresholds in man. It is suggested that differences in biological/toxicological
activity arise primarily from transport from the gas phase to a receptor phase or area,
except for odor detection thresholds where interaction with a receptor(s) is important.

Abbreviations: VC = volatile compound; QSAR = quantitative structure-activity
relationship; NPT = nasal pungency threshold; EIT = eye irritation thresholds; ODT =
odor detection threshold; RD_{50} = upper respiratory tract irritation in mice; ppm = parts
per million; atm = atmospheres

INTRODUCTION

The toxicological and biological activities of gases and vapors includes such processes as upper respiratory tract irritation in mice (Alarie, 1966, 1973), inhalation anesthesia in mice (Davies *et al*., 1974, 1976) and in rats (Won *et al*., 2006), convulsant activity in rats (Eger *et al*., 1999), and eye irritation thresholds, nasal pungency thresholds and odor detection thresholds in man (see reviews in Cometto-Muñiz, 2001, Cometto-Muñiz et al., 2004). Because of the importance of these effects, there have been numerous attempts to obtain equations that correlate these activities and which can be used to predict further values of the activity (Abraham *et al*., 1990, 1998a, 1998b, 2002, 2007, 2008a; Abraham and Acree 2009; Alarie *et al*., 1995 and 1996; Davies *et al*., 1974, 1976; Famini *et al*., 2002; Hau and Connell 1998, Hau *et al*., 1999; Luan *et al*., 2006; Muller and Gref 1984; Roberts 1986; Sewell and Sear, 2004 and 2006).

In any equation that is established, predictions should only be made for volatile compounds, VCs, that lie within the chemical space of the VCs used to construct the equation. The problem with all the equations so far established is that the VCs used to construct the equations are too small in number and too close in variety to provide predictions for a wide range of VCs. For example, quantitative structure-activity relationships (QSARs) have been derived for nasal pungency thresholds (NPTs) using 33 VCs (Hau *et al*., 1999) or 44 VCs (Abraham *et al*., 1998b; Famini *et al*., 2002), all of which are rather simple molecules. The set of 33 or 44 compounds includes no ethers, no fluorocompounds, no bromocompounds, no nitriles, no nitrocompounds, and only one heterocyclic compound (pyridine) so that predictions are severely limited to a few specific types of VC. It is the aim of the present work to ascertain if it is possible to combine several different biological and non-lethal toxicological processes in the same equation, and thus to extend the chemical space of the VCs and the area of possible predictions. Of course, the statistics of any combined equation will not be expected to be as good as those for the separate equations, but the hope is that any combined equation will still be good enough to yield reasonable predictions of biological/toxicological activity of gases and vapors. Note that we use the term 'volatile compounds' rather than

'volatile organic compounds' because we deal with inorganic compounds as well as organic compounds.

MATERIALS AND METHODS

The methods we use are based on two linear free energy relationships, LFERs, equation [1] and equation [2]

$$\mathbf{Y} = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L} \tag{1}$$

$$\mathbf{Y} = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V} \tag{2}$$

The dependent variable, **Y**, is some property of a series of solutes in a given fixed process. For example **Y** might be log (1/NPT) for a series of VCs. The five independent variables, or descriptors, are properties of the VCs as follows (Abraham, 1993; Abraham *et al.*, 2004). **E** is the VC excess molar refraction and reflects the ability of the solute to undergo general dispersion interactions, **S** is the VC dipolarity (plus some polarizability), **A** is the VC hydrogen bond acidity, **B** is the VC hydrogen bond basicity, **L** is the solubility of the gaseous VC in hexadecane at 25°C, expressed as the gas to hexadecane partition coefficient, and **V** is the McGowan characteristic volume. **L** and **V** can be regarded as measures of the size of the VC. The regression coefficients, c, e, s, a, b, l, and v are obtained by multiple linear regression analysis.

Equations on the lines of equation [1] have previously been obtained for eye irritation thresholds (Abraham *et al.*, 1998a), nasal irritation (pungency) thresholds (Abraham *et al.*, 1998b), odor detection thresholds (Abraham *et al.*, 2002), upper respiratory irritation in mice (Abraham *et al.*, 1990), inhalation anesthesia (Abraham *et al.*, 2008a) and convulsant activity (Abraham and Acree, 2009). In the case of convulsant activity, four compounds were more potent than predicted (Eger *et al.*, 1999) from solubility in olive oil (perfluorodimethylcyclobutane, 1,1,1,2,2,3,3,4,5,6,6,6-dodecafluorohexane, bis(2,2,2-trifluoroethyl)ether, and perfluorotoluene). In addition, scores in the Draize rabbit eye test for pure liquids can be converted into scores for the corresponding vapors by the liquid saturated vapor pressure (Abraham *et al.*, 1998a,

1998c). We have included a few VCs for which Draize scores have subsequently been recorded (Takahashi *et al*., 2008). Concentrations for aqueous tadpole narcosis (Bowen *et al*., 2006) have been converted into gaseous concentrations by use of the gas to water partition coefficient (Abraham and Acree, 2007); values of log(1/C), where C is the gaseous narcotic concentration, were used as the function of activity. Only data for the species *Rana temporaria* were used. We could have included data for other tadpole species, but that would have meant another indicator variable for each species, and a more complicated general equation than was necessary.

The data used in the above studies, together with more recent data on upper respiratory irritation in mice (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007), as log (RD_{50}) can all be collected together. RD_{50} is the vapor concentration of a VC in ppm that reduces the rate of breathing of a mouse by 50%. For nasal pungency thresholds, eye irritation thresholds and odor detection thresholds we use log(1/NPT), log(1/EIT) and log(1/ODT), in units of ppm, so that the larger the numerical value, the more potent is the VC. In the case of inhalation anesthesia in mice (Davies *et al*., 1974, 1976) further studies at the same organization were later carried out (Bagnall *et al*., 1977, 1978, 1979a, 1979b, 1979c). However, we have not been able to include these results at all; possibly a different protocol was used in the later studies. We use the original units, rather than converting them all into some common unit, in order to make it easier to check the original data, and in order to make predictions without the necessity of converting units. In any case, all the units used are molar quantities as required (Dearden *et al*., 2009). The units of RD_{50}, NPT, EIT and ODT are ppm (vol/vol) so that by Avogadro's hypothesis, these all correspond to mol/volume. The units of inhalation anesthesia and convulsions are partial pressure, but since PV = RT it follows that log P is proportional to –log V, and, again by Avogadro's hypothesis, this is (the logarithm of) a molar quantity. The end point for inhalation anesthesia in mice (Davies *et al*., 1974, 1976) was given as vol/vol, so again is a molar quantity. Hence all the data we have used are molar quantities.

We were able to collect 720 numerical values for the biological activity of VCs, see Supplementary material. Of course, this is not 720 compounds, because many compounds have more than one entry.

In order that the activity of compounds in two processes can be put on the same scale, it is necessary that there be a constant difference between the activity of corresponding compounds in the two processes. Then this constant difference can be modeled by incorporation of an indicator variable in a general equation. We use equation (1) because that has been the basis for analyses of several measures of biological/toxicological activity, and we choose eye irritation as a 'standard', because it is one of the few processes that refer directly to effects on humans, and because we are particularly interested in sensory irritation – the combination of eye irritation and nasal pungency. Then for any other process, an indicator variable is added to equation (1). If several other processes are included, an indicator variable is needed for each process.

RESULTS

All the data we use is given in the Supplementary Table, together with the VC descriptors used in the calculations. These descriptors have all been obtained from experimental data, as explained before (Abraham *et al*., 2004). We first show how the present method leads to an equation that includes VCs that cover a very large chemical space. The chemical space of a set of VCs can be represented by the descriptors in equation (1) – the larger the numerical variation in the descriptors the larger is the chemical space. If the five descriptors were plotted as points in five-dimensional space, the volume enclosed by the points would be an exact measure of the chemical space. In order to visualize the chemical space, we use principal components analysis, PCA, transform the five columns of descriptor data into five principal components or PCs. The scores for the first two principal components typically contain about 80% of the total information. Then a plot of PC2 against PC1 for a given process will give an indication of the chemical space of the VCs used in that process.

In Fig. 1 is given a plot of PC2 against PC1 for eye irritation thresholds (Abraham *et al*., 1998a), and for inhalation anesthesia (Davies *et al*., 1974, 1976). The chemical space covered by the two sets of VCs is completely different, and so if it were possible to combine the data, the resulting equation would cover a much wider chemical space than either set separately, and would be much more general.

For the analysis of the 720 data points listed in the Supplementary material, all were first included in the regression, and outliers then removed. Our criterion for an outlier was that it deviated by more than 2.8 standard deviations of the regression equation. This criterion was not chosen arbitrarily, but was selected so that we did not remove any VCs in the mouse assay test listed as operating through a physical mechanism (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007); these workers classed VCs into those operating through a physical mechanism and those operating through a chemical mechanism. There were 53 outliers out of 147 VCs in the mouse assay test. These included VCs such as the isocyanates with a very reactive carbonyl group, and α,β-unsaturated compounds known to react with nucleophiles through Michael-type addition reactions (Yarbrough and Schultz 2007; Schultz *et al*., 2007).

As regards odor detection thresholds, ODTs, the terms 'physical' or 'chemical' are not very useful. In an analysis of ODTs, it was found (Abraham *et al*., 2007) that a compound such as octan-1-ol was an outlier, although it cannot be regarded as acting through a 'chemical' mechanism. It was suggested that the terms 'selective' and 'specific' were more appropriate. A selective process is one in which small structural changes in the VC evoke predictable and rather small changes in biological activity, and a specific process is one in which small structural changes in the VC may evoke less predictable and often large changes in biological activity (Abraham *et al*., 2007). The factors that lead to a specific process have not fully been elucidated, although it has been found that a particular maximum unfolded length of about 12 Å leads to enhanced potency (Abraham *et al*., 2002). Of the 64 compounds for which we had ODT values, 20 were outliers. It is known that statistically reasonable equations for log (1/ODT) can only be set up if quite a large number of VCs are omitted (Abraham *et al*., 2007) and so it is no surprise that there are outliers in the ODT set.

The only other outliers were pentane, urea, nicotine and strychnine in the calculated inhalation anesthesia of tadpoles (Abraham and Acree, 2007); urea and nicotine were outliers in the regression equation for aqueous anesthesia of tadpoles (Bowen *et al*., 2006). A summary of the number of VCs in the various processes is in Table 1, and full details are in the Supplementary Table.

Table 1. The number of VCs in the various processes that have been used					
Process	Units	Y	Indicator	Number of VCs	
				Total	Outliers
Eye irritation thresholds	ppm	log(1/EIT)	None	23	0
EIT from Draize scores	ppm	log(D/P^o) ^{a}	Idr	72	0
Odor detection thresholds	ppm	log(1/ODT)	Iodt	64	20
Nasal pungency thresholds	ppm	log(1/NPT)	Inpt	48	0
Inhalation anesthesia in rats	atm	log(1/MAC)	Imac	147	0
Upper respiratory irritation in mice	ppm	log(1/RD$_{50}$)	Ird50	147	53
Gaseous anesthesia in tadpoles	mol/L	log(1/C)	Itad	130	4
Convulsant activity of vapors in rats	atm	log(1/CON)	Icon	44	0
Inhalation anesthesia in mice	vol %	log(1/vol)	Idav	45	0
Total				720	77

^{a} D is the Draize eye score and P^o is the VC saturated vapor pressure.

Application of equation [1] plus the indicator variables shown in Table 1 to the 720 data points led to equation [3], after deletion of the 77 outliers.

Y = -7.805 + 0.056 E + 1.587 S + 3.431 A + 1.440 B + 0.754L + 0.553 Idr +
2.777 Iodt -0.036 Inpt + 6.923 Imac + 0.440 Ird50 + 8.161 Itad +7.437 Icon +   (3)
4.959 Idav
$N = 643$, SD = 0.357, $r^2 = 0.992$, $q^2 = 0.992$, PRESS = 84.536, $F = 6083$, PSD = 0.367

Here, N is the number of data points, SD is the regression standard deviation, r is the correlation coefficient, q and PRESS are the leave-one-out statistics, F is the F-statistic and PSD is the 'predictive standard deviation' (Hawkins, 2004; Abraham *et al*., 2009) PDS is defined similarly to SD; the latter is given by SD = $\sqrt{[SSE/(N -1 -v)]}$ where SSE is the sum of squares of errors and v is the number of independent variables, and PSD =

√[PRESS/(N -1 −v)]. PSD is a very useful statistic and can be taken as a measure of the predictive capability of the equation. It can be seen that the coefficient of the NPT indicator variable is very small (-0.036) so that NPT and EIT values are almost exactly matched and the NPT indicator variable can be removed. The e-coefficient (0.056) is not statistically significant and if this is removed as well, equation [4] results. The r^2 statistic of 0.992 indicates that over 99% of the variance in the data is accounted for. This will include random experimental and biological error, but not, of course, systematic error.

$$Y = -7.839 + 1.620\ \mathbf{S} + 3.431\ \mathbf{A} + 1.413\ \mathbf{B} + 0.759\ \mathbf{L} + 0.578\ \mathbf{Idr} + 2.801\ \mathbf{Iodt}$$
$$+ 6.941\ \mathbf{Imac} + 0.465\ \mathbf{Ird50} + 8.190\ \mathbf{Itad} + 7.452\ \mathbf{Icon} + 4.972\ \mathbf{Idav}$$
$$N = 643,\ SD = 0.357,\ r^2 = 0.992,\ q^2 = 0.992,\ PRESS = 83.998,\ F = 7199,\ PSD = 0.365$$

(4)

The F-statistic is often used as a criterion for removing descriptors; the larger the F-statistic the more efficient is the equation. A more powerful method is through the Akaike information criterion, AIC, (Cavanaugh , 1997) which takes into account the number of descriptors, p, the number of data points, N, and the regression residual sum of squares, RSS, also known as SSE, the error sum of squares,

$$AIC = 2p + N\ [\ln(2*\pi*RSS\ /\ N) + 1]$$

(5)

The smaller the value of AIC, the more efficient or economic is the model. Note that equation [5] can only be applied to a set of equations with the same number of data points. We give in Table 2 details of the application of the AIC criterion to equation [3] as we remove successively the least important descriptor. There is little improvement in efficiency if the descriptors **Inpt** and **E** are removed, but removal of the next least important descriptor, **Ird50**, leads to a very considerable increase in AIC. The AIC criterion marks equation [4] as the most efficient (as does the F-statistic). Very little can be deduced from the values of r^2 or SD.

Table 2. Determination of the efficiency of equations					
Equation	P	SD	r^2	F	AIC
Equation [3]	13	0.357	0.992	6083	513.4
Remove **Inpt**	12	0.357	0.992	6599	511.6
Remove **Inpt, E,** Equation [4]	11	0.357	0.992	7199	510.5
Remove **Inpt, E, Ird50**	10	0.375	0.991	7159	573.9

The statistics of equation [4] are practically identical to those of equation [3] and so can be used for the prediction of sensory irritation thresholds (SIT) in humans. In this case, all the other indicator variables can be set to zero to leave equation [6] as the most soundly-based equation for the prediction of sensory irritation thresholds in humans, as log(1/SIT), with an estimated predictive error of 0.36 log units.

$$\mathbf{Y} = -7.839 + 1.620\ \mathbf{S} + 3.431\ \mathbf{A} + 1.413\ \mathbf{B} + 0.759\ \mathbf{L} \tag{6}$$

We also investigated the use of equation [2] in the analysis of activity. Although equation [1] is usually better than equation [2] for the correlation and prediction of processes involving transfer of gases to a condensed phase, equation [2] has an advantage that the descriptor **V** can be calculated from structure. Thus in cases where the **L** descriptor cannot be obtained, equations [7] and [8] can be used to predict sensory irritation thresholds with little loss in predictive capability (PSD = 0.40 log units). In equation [7] isostearyl alcohol was an additional outlier in the EIT from Draize scores data set.

$$\mathbf{Y} = -8.538 + 1.098\ \mathbf{E} + 2.174\ \mathbf{S} + 3.707\ \mathbf{A} + 1.459\ \mathbf{B} + 2.663\ \mathbf{V} + 0.621\ \mathbf{Idr} +$$
$$2.820\ \mathbf{Iodt} + 6.936\ \mathbf{Imac} + 0.469\ \mathbf{Ird50} + 8.220\ \mathbf{Itad} + 7.437\ \mathbf{Icon} + 5.051\ \mathbf{Idav} \tag{7}$$
$$N = 642,\ SD = 0.391,\ r^2 = 0.991,\ q^2 = 0.990,\ \text{PRESS} = 100.588,\ F = 5503,\ \text{PSD} = 0.400$$

$$\mathbf{Y} = -8.538 + 1.098\ \mathbf{E} + 2.174\ \mathbf{S} + 3.707\ \mathbf{A} + 1.459\ \mathbf{B} + 2.663\ \mathbf{V} \tag{8}$$

DISCUSSION

When data for the various end points shown in Table 1 are fitted to equation [1], equations are obtained with different intercepts (c) and different coefficients (e-l). How all the data can be expressed in one equation is shown in Fig.2, that is based on the simple equation [9].

$$\mathbf{Y} = \text{m } \mathbf{X} + \text{c} \tag{9}$$

Two sets of data points are shown in Fig. 2, those for equation B having a different slope and very different intercept to those for equation A. An indicator variable adjusts the points for equation B so that both sets of points have the same intercept. Then it is possible to derive an equation for the combined set of points with an 'average' slope. The SD value for the combined equation will not be as good as the separate SD values, but provided that the separate equations have slopes that are not too far apart, the combined equation may be judged to be reasonable, and, of course, will cover a much larger range of values.

The coefficients of the indicator variables in equation [3] yield information as to the sensitivity of the various processes, for the specific cases where the same units are used, and where the form of the dependent variable is the same. From Table 2 it can be seen that a number of processes conform to this, and can then be ranked for sensitivity. The indicator variable for nasal pungency irritation is very nearly zero, and so, on the given experimental protocol, the sensitivity towards irritants is the same for eye irritation and nasal pungency. The mouse assay is a little more sensitive than sensory irritation, **Ird50** = 0.44 log units, and the olfactory system for odor detection thresholds is very much more sensitive than sensory irritation or the mouse assay, **Iodt** = 2.77 log units.

Our preferred equations for sensory irritation thresholds, equation [4] and equation [6], are statistically very good, they cover a very wide range of VCs, and have a predictive ability of about 0.36 log units in log (1/SIT). This is good enough for the prediction of SIT values for a host of atmospheric pollutants. Although equation [4] covers a very large range of VCs, great care must still be taken over compounds that

might act through a specific mechanism, because there is no reason why compounds that act by a specific mechanism in one test to one species should act in the same way in another test to another species. Amines and isocyanates were classed as acting via a chemical mechanism in the mouse assay, (Alarie *et al*., 1995 and 1996; Nielsen *et al*., 2007) and they might act in a similar way in an eye irritation threshold test, but this does not necessarily follow from the mouse assay results. In addition, we have recently shown that on ascending a homologous series of VCs, for example n-alkyl acetates or n-alcohols, the sensory irritation, i.e., chemesthetic, activity of the VC does not continually increase, but a point is reached at which the activity begins to decrease (Cometto-Muñiz *et al*., 2005a, 2005b, 2006 and 2007, Cain et al., 2006) This 'cut-off' is possibly due to an effect of VC size (perhaps the length of a VC) that inhibits interaction with human chemesthetic receptors (Cometto-Muñiz et al., 2007, Cometto-Muñiz and Abraham, 2008). Hence care must be taken over the use of equation [4] for the prediction of sensory irritation thresholds of large VCs. Furthermore we note that the absolute value of sensory irritation thresholds specifically refer to a given experimental protocol (Cometto-Muñiz et al., 2000 and 2002).

Finally, we comment on the implications of the general equation [4] for the mechanism of non-lethal toxic and biological action of VCs. It has been suggested (Abraham *et al*., 1994) that the activity of gaseous VCs takes place through a two-stage mechanism: (1) a VC is transferred from the gas phase to a receptor phase or area, and (2) the VC then interacts with a receptor. The observation that VC activities of non-reactive compounds in a wide variety of biological systems can be well correlated by the same equation indicates that the main step in the two-stage mechanism is transfer from the gas phase to receptor phases or areas. The receptors themselves discriminate only marginally between the different VCs. The coefficients e-l in equation [4] are certainly comparable with coefficients in equation [1] for transfer from the gas phase to phases such as wet pentanol (Abraham *et al.,* 2008b), wet butyl acetate (Sprunger *et al*., 2008), and, possibly quite significantly, the peptide model N-methylformamide (Abraham *et al.,* 2009). The coefficients are not far from transfers from the gas phase to the biological phases brain and muscle (although some way from fat), as shown in Table 3 (Abraham and Ibrahim, 2006; Abraham *et al*., 2006a and 2006b). Naturally, there will be differences in the final

biological phase (the receptor phase or area) and so at a more detailed level than our general equation represents, various equations on the lines of equation [1] are necessary to correlate the different processes.

In the case of odor detection thresholds, the large number of outliers to equation [4] suggests that interaction with a receptor, stage two, now plays a significant part, and that the receptor(s) does discriminate between VCs (see, for example, Malnic, 2007).

The supplementary table contains a full list of all the compounds studied, the corresponding biological and toxicological data and the descriptors used in the regression equations.

Table 3. Coefficients in equation [1] for a number of systems						
System	c	e	s	a	b	l
Equation [3]	-7.80	0.03	1.58	3.42	1.37	0.757
Gas to wet pentanol	-0.11	0.00	1.19	3.61	1.67	0.721
Gas to wet butyl acetate	-0.66	0.06	1.67	3.37	0.82	0.832
Gas to N-methylformamide	-0.25	-0.14	1.66	4.15	0.82	0.739
Gas to brain	-0.99	0.26	0.41	3.36	2.02	0.591
Gas to muscle	-1.04	0.21	0.72	3.24	2.47	0.463
Gas to fat	-0.05	0.05	0.73	1.78	0.33	0.743

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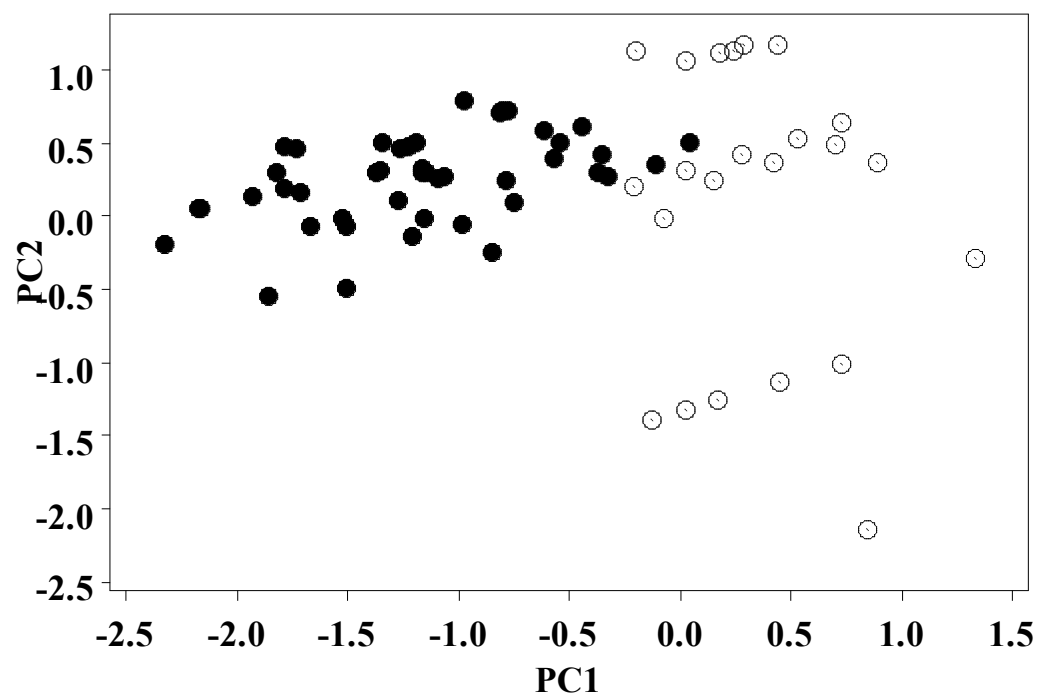
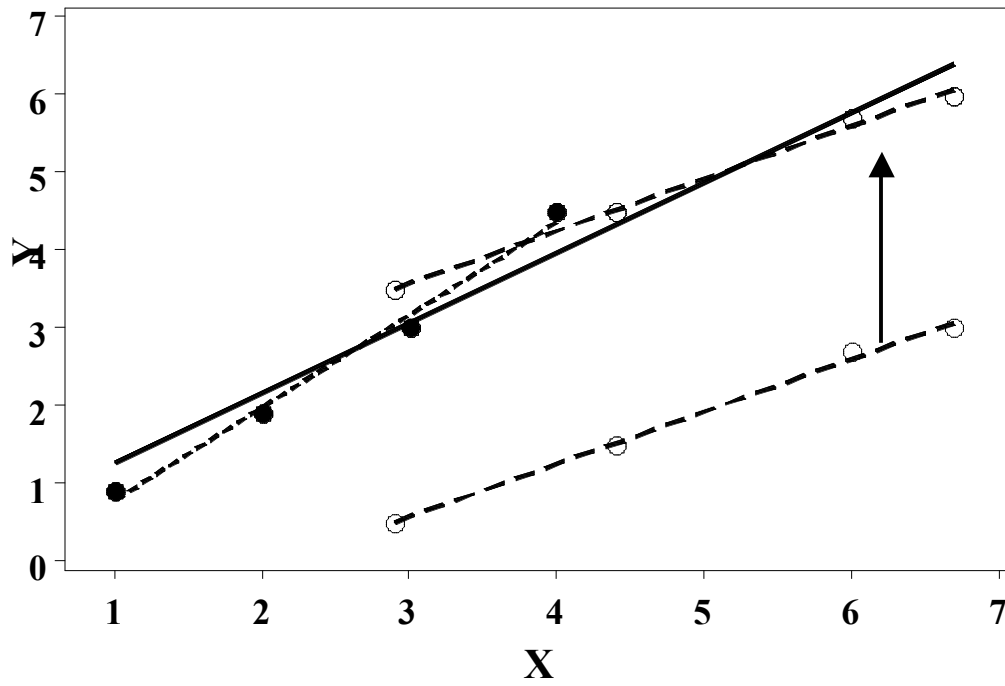Fig. 1. Plot of PC2 against PC1 for eye irritation ○ and inhalation anesthesia (Davies) ●.

Fig. 2. Plots of equations of the form Y = mX + c; ● equation A; ○ equation B; vertical

arrow ⟶ shows the effect of an indicator variable. Dashed lines are for the separate

equations, full line for the combined equation.