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ESTIMATING THE ACUTE TOXICITY OF WATERBORNE CHEMICALS TO TROUT FROM MEASUREMENTS OF MEDIAN LETHAL DOSE AND THE OCTANOL-WATER PARTITION COEFFICIENT

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CALCUL DE LA TOXICITE AIGUË DES PRODUITS CHIMIQUES D'ORIGINE HYDRIQUE POUR LA TRUITE D'APRÈS LES MESURES DE LA DOSE LÉTHALE MÉDIANE ET DU COEFFICIENT DE PARTAGE OCTANOL/EAU

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Running Head: Predicting LC50s

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RÉSUMÉ

La mesure de la dose léthale médiane (LD50) des produits chimiques pour le poisson est une méthode plus simple, plus rapide et moins coûteuse que la détermination des concentrations léthales (LC50). Étant donné que la dose est contrôlée, la LD50 peut donner une meilleure idée des rapports entre la structure et l'activité. Toutefois, les LC50 sont beaucoup utilisés dans l'évaluation des risques pour les milieux aquatiques. Par conséquent, on a mesuré la LC50 et la LD50 de 48 produits organiques pour la truite arc-en-ciel dans le but de déterminer si la LD50 peut permettre de préduire la LC50. Une simple régression linéaire des données transformées en logarithmes a donné le meilleur ajustement ($r = 0,70$) mais ne rendait compte que de 50 % de la variabilité de la LC50. La LC50 était également fortement corrélée aux mesures de la taille des molécules (poids moléculaire (PM, $r = -0,90$) et parachor ($r = -0,89$)) et du coefficient de partage eau-lipides (coefficient de partage octanol-eau, K_{ow}; $r = -0,73$)). On a donc étudié la possibilité d'inclure ces facteurs dans une analyse de régression multiple. Comme le PM et le parachor sont corrélés négativement à la LD50 ($r = -0,62$ et $-0,58$, respectivement), ils ne constituent pas de véritables variables indépendantes et n'ont pas été utilisés. Toutefois, il n'y avait aucun rapport entre le K_{ow} et la LD50 et une analyse de régression multiple utilisant à la fois la LD50 et le K_{ow} a permis de faire une prédiction beaucoup plus précise ($r = 0,92$) de la LC50 que lorsque chaque facteur est utilisé séparément. Par conséquent, On a pu prédire la LC50 à partir de la LD50 en tenant compte du partage des produits chimiques entre l'eau et les lipides.

MOTS CLÉS : QSAR; LC50; LD50; K_{ow}; MODÈLE

ABSTRACT

Measurements of the median lethal dose (LD50) of chemicals to fish provide a simpler, faster, and less expensive alternative to median lethal concentrations (LC50s). Since dose is controlled, LD50s may be a better basis for structure activity relationships. However, LC50s are extensively used in aquatic hazards assessments. Therefore, LC50s and LD50s for rainbow trout of 48 organic chemicals were measured to determine whether LC50s could be predicted from LD50s. A simple linear regression of log transformed data provided the best fit ($r = 0.70$), but it accounted for only 50% of the variability in LC50s. LC50s were also strongly correlated to measures of molecular size (molecular weight (MW; $r = -0.90$) and Parachor ($r = -0.89$)) and of water-lipid partitioning (Octanol-water partition coefficient, K_{OW}; $r = -0.73$)). Hence, inclusion of these factors in a multiple regression analysis was examined. Since MW and Parachor were negatively correlated to LD50s ($r = -0.62$ and -0.58 respectively), they were not true independent variables and were not used. However, there was no relationship of K_{OW} to LD50s, and a multiple regression analysis using both LD50s and K_{OW} predicted LC50s with a greater certainty ($r = 0.92$) than either factor alone. Therefore, LC50s could be predicted from LD50s when partitioning of chemicals from water to lipid was recognized.

KEY WORDS: QSAR; LC50; LD50; K_{OW}; MODEL

INTRODUCTION

Hazard assessments of aquatic pollutants require measurements or estimates of chemical toxicity to aquatic biota. For acute lethality, traditional tests to measure LC50s are rather cumbersome, in that chemicals must be added to water at constant concentrations, and these concentrations must be measured repeatedly to assure reliable comparisons of cause and effect. For chemicals that are expensive, of low water solubility, or difficult to measure in water, traditional aqueous toxicity tests may be impractical.

A more fundamental and important objection to LC50s is that 'dose' is unknown: they estimate 'expressed' rather than 'inherent' toxicity [1]. Inherent toxicity is toxicity unmodified by any factor, and should be described in terms of the concentration of the chemical at the site of toxic action. Expressed toxicity is inherent toxicity modified by factors that change the amount of chemical reaching the site of toxic action and the sensitivity of the receptor. It is often described as a concentration in a medium other than that of the receptor. For example, LC50s refer to the concentrations of chemicals in water rather than in a target tissue. Measures of inherent toxicity are essential for development of accurate quantitative structure activity relationships (QSARs), since expressed toxicity may reflect a structural interaction with chemical accumulation or metabolism, rather than with the actual toxic mechanism.

The injection of chemicals into fish should avoid these problems [2]. It is less effort, uses much less chemical and requires no analytical work. Furthermore, the dose administered is known, giving more precise and accurate estimates of inherent toxicity, unmodified by processes such as dissociation or hydrolysis of chemicals in water.

Injection of chemicals into fish mimics mammalian lethality tests in that the route of exposure is the same. Hence, it is not surprising that estimates of inherent toxicity in fish and mammals are similar: the median lethal dose for trout of chemicals injected intraperitoneally (IP LD50) is closely correlated to IP LD50s for rats and mice [3]. Therefore, there is a possible further advantage of measuring LD50s: the application of mammalian test data to aquatic hazard assessments.

Since a fundamental question of hazard assessments is "What chemical level in water is harmful to fish?", LD50s must ultimately be translated into LC50s. While LD50s are strongly correlated among widely differing species, the relationships between LD50s and LC50s are weaker, even when comparing values within one species [3,4]. The problem is likely a consequence of uptake across the gills. To recognize the possible role of partitioning of chemicals from aqueous to lipid phases (gill tissue) in traditional aqueous toxicity tests, Hodson [3] tried to incorporate octanol-water partition coefficients (K_{OW}) in equations relating LC50s to LD50s. Since the total number of test data was small and the range of their values rather limited, correlations were not improved. This paper

analyzes a larger data set and compares LC50s and LD50s by multiple linear regression analysis to test the null hypothesis that there is no relationship between inherent and expressed toxicity of chemicals to fish. The influence of water lipid partitioning is recognized through inclusion of K_{OW} in the equations; molecular weight (MW) was also studied since molecular size could influence chemical uptake across gills. Parachor (molar volume) was chosen as a second measure of molecular size since it accounts for the different volume contributions of each unique substituent. Compounds with equivalent molecular weights may have quite different volumes.

MATERIALS AND METHODS

Design:

Measurements of LC50s for rainbow trout (Salmo gairdneri) were compared to LD50s by linear regression analyses after log transformations. The ability to accurately predict LC50s and to improve on predictions by including K_{OW}, MW and Parachor was assessed by comparing correlation coefficients, residuals and 'outliers' (see below).

Data:

Measurements of LC50s, LD50s and K_{OW} were taken from Hodson et al. [2] and Hodson [3]. To expand the data base, additional tests were conducted for both LD50s and LC50s. Chemicals added to the previous data set were

chosen to provide a wider range of solubilities and toxicities. These included solvents and tributyltin oxide (TBTO), a specific biocide. For some chemicals previously tested, either the LC50 or LD50 were measured to complete a pair. The LC50 for one chemical (dimethylformamide) was taken from the literature (Table 1).

All tests were conducted in triplicate using the same source of fish, the same test conditions and the same chemical purification methods used by Hodson et al. [2]. There are no times indicated on the LC50s or LD50s since tests were conducted for four days or until all mortality had ceased for at least 24 h; these values are equivalent to incipient lethal levels. For most chemicals, mortality was complete within 48 h.

Values for log K_{OW} were obtained from Hansch and Leo [5] unless otherwise indicated in the summary tables (Table 1), and estimates for Parachor were taken from Quayle [6] or calculated by addition of his substituent constants.

Statistics:

The LC50s were compared to LD50s, K_{OW}, MW and Parachor by linear regression analyses [7] after log transformations of all data. The transformations were necessary since standard deviations of measured toxicity (mean of three replicate LC50s or LD50s) increased with the size of the mean; dependance on the mean was removed by the transformation. The transformation also allowed the statistical comparison of data with widely differing values; for example, LC50s spanned eight orders of

magnitude.

For multiple regression analyses or when polynomials were applied to data, the inclusion of a variable in an equation was determined by the statistical significance of slopes and regressions. A variable was included only when the probability that a slope was not different from zero was less than 0.05.

Chemicals that did not appear to fit specific regressions were termed 'outliers' and were identified by setting an arbitrary limit of one order of magnitude difference between a predicted and observed LC50. In other words, if the predicted value was more than 10 times higher or lower than the observed value, the LC50 was an outlier.

The data reported in Table 1 formed the basis for all regressions. While the chemicals are grouped into classes, the regressions 'lumped' them together, without regard for class. Since some values are missing, the regressions have varying numbers of chemicals included, depending upon which factors are being compared. This may introduce some bias into the analyses if compounds with extreme properties are left out of some comparisons. Chemicals for which values are missing were usually too insoluble to test, either when added to water in aqueous tests or added to saline, oil, or dimethylformamide in injection tests; some were also too expensive to add to continuous-flow aqueous tests. Therefore, regressions between different factors may not apply to all chemicals.

RESULTS AND DISCUSSION

A repeat of the regression reported by Hodson [3] between LC50s and IP LD50s gave somewhat improved results. By increasing the sample size from 14 to 25, the correlation coefficient increased to 0.70 (Figure 1) from 0.60 [3]. However, this still leaves about 50% of the deviations from the regression unaccounted for. In fact, 13 of the 25 compounds included were outliers, i.e. the predicted values were more then 10 times higher or lower than the observed (Table 2). Many of these were either chlorinated compounds of relatively low solubility, or solvents, which are extremely soluble in water. The distribution of residuals from Figure 1 suggested a curvilinear relationship, in large part due to the very low toxicity of water miscible solvents (acetone, ethanol, dimethylformamide) in aqueous tests. However, a polynomial equation that included the square of LD50s only increased r to 0.74 and the slope for the squared term was non-significant (t_b = 1.668). Hence, the linear relationship was the best fit.

Since linear regression analysis assumes that the independent variable is fixed and measured without error [7], the regression of Figure 1 may be biased. Ricker [8] provides an alternative method, a 'functional' regression analysis. In standard regression analysis, deviations from regressions are calculated by subtracting the estimated LC50 from the observed, i.e. the distance from the observed value to the regression

line on an axis parallel to the Y axis. In functional regression analysis, the deviation is the distance from each observation along a line perpendicular to the regression line. The correlation coefficients are the same, but both the slope and intercept are altered. The functional regression for Figure 1 is:

$$\log LC50 = 1.693 \log LD50 - 1.9965$$

The comparison of LC50s to LD50s within one species, the rainbow trout, gave a correlation coefficient very similar to that observed for correlations of bluegill (Lepomis gibbosus) or fathead minnows (Pimephales promelas) LC50s to rat LD50s [4].

The transport of chemicals from water across gill membranes is an integral part of intoxication by waterborne chemicals, but not of intoxication by injected chemicals. Hence, the variability in Figure 1 might be accounted for by regressions of LC50s on factors describing molecular size (MW, Parachor) or water-lipid partitioning (K_{OW}). If these factors were not correlated to LD50s (i.e. they are true independent variables), then a multiple regression analyses could estimate LC50s from inherent toxicity modified by chemical availability. Therefore, MW, Parachor and K_{OW} were correlated by linear regression analysis with both LC50s and LD50s to establish whether these factors were related to LC50s and whether they were truly independent of LD50s.

An inverse relationship of LC50s to all three factors was observed

(Table 3, Figures 2 to 4). The strongest correlations were between the log of LC50s and the log of MW and Parachor; the correlation coefficients were about equal and accounted for about 80% of the variability in LC50s. However, a reasonably strong inverse relationship was also found between log LD50s and the log of MW and Parachor; correlation coefficients were -0.62 and -0.58 respectively. Consequently, LD50s, MW and Parachor could not be considered independent variables and could not be used together in equations predicting LC50s.

An inverse correlation was also found between K_{OW} and LC50s although it was weaker than the relationship to MW and Parachor (Table 3), accounting for only about 50% of the variation in LC50s. As well, there was no relationship between LD50s and K_{OW} (Figure 4b). While an inverse regression is portrayed, neither the slope (t_b = -0.98) nor the regression (F_{reg} = 0.97) were statistically significant and the distribution of residuals did not suggest an alternative curvilinear relationship. Therefore, K_{OW} and LD50s were essentially independent of each other and could be used in a multiple linear regression analysis of LC50s.

Compared to the regression of LC50s on LD50s, the regression of LC50s on K_{OW} was stronger; fewer chemicals were considered outliers (Table 2). These no longer included the hydrophobic chlorinated compounds but did include water miscible solvents plus TBTO, hydroquinone and p-aminophenol, chemicals with specific toxic actions. Considering these unusual toxicities and solubilities, it is possible that a multiple

regression that included both variations in inherent toxicity and water-lipid partitioning might account for the unexplained variability.

The multiple regression analysis generated an equation describing a plane of response (Figure 5): LC50s increased with LD50s and decreased with K_{OW}. The correlation coefficient ($r = 0.92$) indicates a real improvement in predicting LC50s relative to regressions based on LD50s or K_{OW} alone. Of the total variation in the data, 84% was accounted for by variations in inherent toxicity (LD50s) or partitioning between water and lipid (K_{OW}). In other words, the equation predicts LC50s on the basis of changes in estimated potency (LD50) and chemical availability (partitioning). Coincidentally, about 84% (21 of 25) of the predicted LC50s fell within one order of magnitude of the test values.

While the slopes of Figure 5 were highly significant ($t_{b\ KOW} = -6.891$; $t_{b\ LD50} = 5.465$) as was the regression ($F_{reg} = 57.98$), improvements to the fit may be possible. However, the obvious factor, curvilinearity in the relationship to LD50s, did not improve the multiple regression.

The residuals from the multiple regression demonstrate fewer outliers than were observed for simple linear regressions (Table 2). The outliers no longer include substances with extreme high or low solubilities (solvents, chlorinated benzenes) or substances with unexpectedly high toxicities (e.g. p-aminophenol). These were apparently eliminated by simultaneously considering partitioning and inherent toxicity. Instead, outliers consisted of compounds with a specific or unusual mode of toxic

action. Pentachlorophenol interferes with the production of energy through effects on oxidative phosphorylation [9], while TBTO has major effects on membranes and can also impair oxidative phosphorylation [10]. The toxicity of p-cyanophenol is less than predicted from its LD50 and K_{OW} values and the cause is unknown. One possible reason may be metabolism. If p-cyanophenol is metabolized at a rate close to its rate of uptake, the accumulation of the toxic form may be very slow, thereby lowering the apparent toxicity more than would be expected from partitioning. The same may be true for hydroquinone: we observed a spontaneous degradation in solutions exposed to light; the solution changed from colorless to pink. Therefore, degradation in aqueous tests may have decreased the concentration and/or availability of the toxic form.

Removal of outliers from the data set of Figure 5 and recalculation of the multiple regression gave an equation in which LC50s were somewhat more sensitive to K_{OW} and less sensitive to LD50s (Table 4). The correlation coefficient improved to 0.97 and the range of residuals shrank considerably: all estimated LC50s were within a factor of five of the observed values and there were no new outliers.

While the recalculated equation gives a far more certain estimate of LC50s, it would be inappropriate to use in a routine screening of unknown chemicals. Since there is little knowledge of mode of toxicity, it is not yet possible to determine in advance which chemicals are appropriate for this equation and which are not. Therefore, the former equation,

despite its greater uncertainty, is a more practical estimate of the LC50. As with the equation relating LC50s to LD50s alone, the equation should be expressed as a functional regression.

While the three-way comparison accounted for 84% of the variability in LC50s, the remaining 16% might still be reduced, perhaps through improved methodology. In particular, the assumption that injecting chemicals intraperitoneally gives an unbiased estimate of inherent toxicity needs to be re-examined. The peritoneal cavity is an expandable space containing highly vascular tissues such as the digestive tract, liver and kidney. The injection of a bolus of saline, oil or some other carrier brings a chemical solution in contact with these vascular surfaces. Presumably, the chemical is absorbed with the carrier or is partitioned from the carrier across membranes into blood. Therefore, the absorption of chemicals from the peritoneal cavity may be very much like the uptake of chemicals from water across the gills. Hence, we should expect to see the kinetics of chemical uptake affecting LD50s as they affect LC50s; mechanisms of toxicity of chemicals acting on gills may also be similar to chemical effects on internal organs.

Unpublished studies of chemical kinetics by D.G. Dixon support this contention. Radiolabelled phenol in saline and benzene in oil are taken up into the blood of rainbow trout at different rates after intraperitoneal injection or intragastric gavage (Figures 6A & B). Not only did route of administration affect rates of uptake, but rates varied between the two test chemicals, either due to different rates of

penetration of membranes or different partitioning coefficients between tissue (lipid) and saline and between tissue and oil. The appearance of a chemical in blood, and presumably the site of toxic action, followed a curve, rising fairly quickly after injection and then decaying at different rates. Hence, LD50s do involve a kinetic exposure, albeit a different one relative to LC50s.

Despite the kinetic phase, however, IP LD50s are not correlated to K_{OW}, suggesting that kinetics may not be the problem per se. Rather, it may be the absolute amount of chemical in the body that is of importance, a factor controlled by intraperitoneal injection. For LC50s, the rate at which the levels in the body increase determine the body burden achieved within the time limits of the toxicity test. Since this rate varies with K_{OW} [12], K_{OW} controls the LC50.

The prediction of LC50s from LD50s and K_{OW} is intuitively satisfying, in that the two major determinants of effects, inherent toxicity and availability, are included. However, the three variable equation represents only a marginal improvement over simple linear regressions of LC50s on MW or Parachor alone. Molecular size appears to integrate both toxicity and availability, i.e. both the ability to penetrate membranes as well as the strength of interactions between the chemical and a substrate. This would make particular sense for those chemicals interfering with membranes or enzymatic reactions involving stereospecific interactions. Therefore, application of molecular size to

estimating LC50s deserves further attention. However, Parachor gave no real advantage over MW and MW itself may be limited to a narrow range, since toxicity apparently decreases at MW >600 daltons [14,15]. An alternative for very large molecules may be 'apparent surface area' as recommended by Opperhuizen et al. [15].

CONCLUSIONS

This paper has demonstrated that:

1. There is no support for the null hypothesis of no relationship between inherent and expressed toxicity of chemicals to fish. LD50s are good estimators of LC50s when water-lipid partitioning is recognized.

2. Given an LD50 and an octanol-water partition coefficient, the LC50 of 84% of the tested chemicals can be predicted within one order of magnitude.

3. Given previously demonstrated correlations of fish and mammalian LD50s, measurements of fish LD50s provide a mechanism for using mammalian data to estimate LC50s for aquatic hazard assessments.

4. Simple linear regressions of LC50s on measures of molecular size may be an alternative to multiple regressions on LD50s and K_{OW} since size appears to integrate effects on both chemical uptake and toxicity.

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Table 1. Test chemicals, their properties, and their acute lethality to rainbow trout.

CHEMICALS	Log P	Molecular Weight	Parachor	IP LD50 (mmoles/kg)	LC50 (mM)
Substituted phenols					
phenol	1.49	94.1	222.3	4.34	0.103
p-aminophenol	0.04	109.1	255.3	>3.34 *1	0.011
p-cyanophenol	1.60	119.2	233.3	0.18	0.190
p-methoxyphenol	1.34	124.1	297.6	2.88	0.230
p-phenoxyphenol	3.50	186.2		0.87	
p-methylphenol (p-cresol)	2.25	108.2	260.2	0.73	0.069
p-methylaminophenol ion (metol)		172.0	295.3	0.58	0.0024
p-nitrophenol	1.91	139.1	286.0	0.34	0.057
2,4 dinitrophenol	1.51	184.0	347.4	0.036	0.026
1-napthol	2.70	144.0	329.4	5.15	
hydroquinone	0.59	110.0	242.1	0.169	0.0058
p-hydroxybenzoic acid	1.58	138.1		1.01	>0.72 *
p-hydroxybenzoyl alcohol	0.20	124.2		0.70	
m-chlorophenol	2.50	128.6	262.0	5.04	
p-chlorophenol	2.42	128.6	262.0	0.91	0.0148
2,4 dichlorophenol	3.08	163.0	301.7	2.43	0.016
2,6 dichlorophenol	2.88	163.0	301.7	8.82	0.016
2,4,6 trichlorophenol	3.62	197.5	341.4	1.07	0.0029
pentachlorophenol	5.12	266.4	422.3	0.13	0.0006
p-chlorothiophenol	3.20	144.6	291.2	1.26	
trifluoro p-cresol	2.35	162.1	292.0	0.27	
Substituted benzenes					
benzene	2.15	78.1	206.2	25.8	0.277
toluene	2.69	92.0	245.7	11.0	
chlorobenzene	2.84	112.6	244.1	9.68	0.066
o-dichlorobenzene	3.38	147.0	280.0	7.45	0.017
m-dichlorobenzene	3.38	147.0	281.0	9.8	
p-dichlorobenzene	3.38	147.0	279.5	10.1	0.0099
1,2,3 trichlorobenzene	4.26	181.5	323.6	8.9	
1,2,4 trichlorobenzene	4.26	181.5	323.6	9.8	
1,3,5 trichlorobenzene	4.26	181.5	323.6	30.5	
1,2,3,4 tetrachlorobenzene	4.46	215.9	365.0	5.1	0.0023
1,2,3,5 tetrachlorobenzene	4.50	215.9	365.0	7.7	0.0071
pentachlorobenzene	5.19	250.3	403.2	5.8	
hexafluorobenzene	2.29	186.0	278.1	19.1	
Substituted anilines					
aniline	0.90	93.1	235.2	14.3	0.389
p-chloroaniline	1.83	127.6	264.5	*	0.128
3,4 dichloroaniline	2.69	162.0	304.2	8.07	0.012
Miscellaneous					
ethanol	-0.26	46.0	126.8	137.0	173.0
acetone	-0.30	58.0	161.7	45.9	91.5

propylene glycol		76.0	189.3	200.0	
dimethylformamide	-1.01	73.1	172.8	90.6	144.3 [3]
dimethylsulfoxide		78.1		137.0	
chloroform	1.97	119.5	183.4	4.22	0.51
carbon tetrachloride	2.64	153.8	219.8	17.7	
kepone	3.45	490.7		0.11	
pyridine	0.65	79.1	197.4	8.24	
1-methylnapthalene		142.2	353.8	20.5	
tributyltinoxide	3.20 [2]	596.2	1201.8	0.022	0.000002

[1] * = solubility problems
[2] from reference [12]
[3] from reference [13]

Table 2. Compounds with observed LC50s more than one order of magnitude different from values predicted from linear regression analyses (= 'outliers').

	INDEPENDENT VARIABLES		
	IP LD50	K_{OW}	IPLD50, K_{OW}
COMPOUND:	p-nitrophenol	p-aminophenol	
	2,4, dinitrophenol	hydroquinone	hydroquinone
	p-cyanophenol		p-cyanophenol
	2,6 dichlorophenol		PCP
	3,4 dichloroaniline		
	o-dichlorobenzene		
	p-dichlorobenzene		
	1,2,3,4 tetrachlorobenzene		
	1,2,3,5 tetrachlorobenzene		
	acetone	acetone	
	ethanol	ethanol	
	DMF	DMF	
	TBTO	TBTO	TBTO

Table 3. The relationship between the acute toxicity to fish of chemicals and measures of molecular size and water-lipid partitioning.

X	Y	Y intercept	Slope	t_b[1]	F_{reg}[2]	r[3]	N[4]
log MW	log LC50	12.306	-6.384	-10.54	111.0	-0.90	28
	log LD50	6.358	-2.693	- 5.21	27.15	-0.62	46
log Parachor	log LC50	19.267	-8.448	-10.13	102.7	-0.89	28
	log LD50	9.213	-3.524	- 4.49	20.19	-0.58	41
log K_{OW}	log LC50	0.376	-0.779	- 5.42	29.35	-0.73	27
	log LD50	0.710	-0.093	- 0.98	0.97	-0.15	42

[1] t_b = calculated students 't' statistic for tests of significance of the slope.

[2] F_{reg} = F statistic from an analysis of variance for tests of the significance of the regression.

[3] r = correlation coefficient

[4] N = number of paired observations

Table 4. The relationship between LC50s, K_{OW}, and LD50 with and without outliers.

ALL COMPOUNDS:

$\log LC50 = -0.1014 - 0.6846 \log K_{OW} + 0.8315 \log LD50$

$r = 0.917 \qquad N = 25^1$

$F_{reg} = 57.98$

Range of residuals: -1.7282 - 1.1888

(.018 - 15.4 x predicted)

REMOVE HYDROQUINONE, p-CYANOPHENOL, PCP AND TBTO

$\log LC50 = 0.3342 - 0.768 \log K_{OW} + 0.5727 \log LD50$

$r = 0.97 \qquad N = 21$

$F_{reg} = 126$

Range of residuals: -0.6978 - 0.5652

(.20 - 3.7 x predicted)

[1] N was reduced from 28 due to solubility problems in toxicity tests (Table 1)

FIGURE CAPTIONS

Figure 1. The relationship between LC50s and IP LD50s of rainbow trout. N = 25; r = 0.70; t_b = 4.760; F_{reg} = 22.655.

Figure 2. The relationship between molecular weight (MW) and either LC50s or IP LD50s. Statistics for these regressions are presented in Table 3.

Figure 3. The relationship between Parachor and either LC50s or IP LD50s. Statistics for these regressions are presented in Table 3.

Figure 4. The relationship between octanol-water partition coefficients (K_{OW}) and either LC50s or IP LD50s. Statistics for these regressions are presented in Table 3.

Figure 5. The relationship between IP LD50s, octanol-water partition coefficients (K_{OW}) and LC50s of rainbow trout. N = 25; r = 0.92; t_b LD50 = 5.465; t_b Kow = - 6.892; F_{reg} = 57.98.

Figure 6. The effect of route of administration (intraperitoneal, O- - -O ; oral, ●——●) on the accumulation of ^{14}C-labelled phenol (A) or benzene (B) in the blood of rainbow trout. Each point represents the mean of eight fish with the 95% confidence interval.

Fig 1

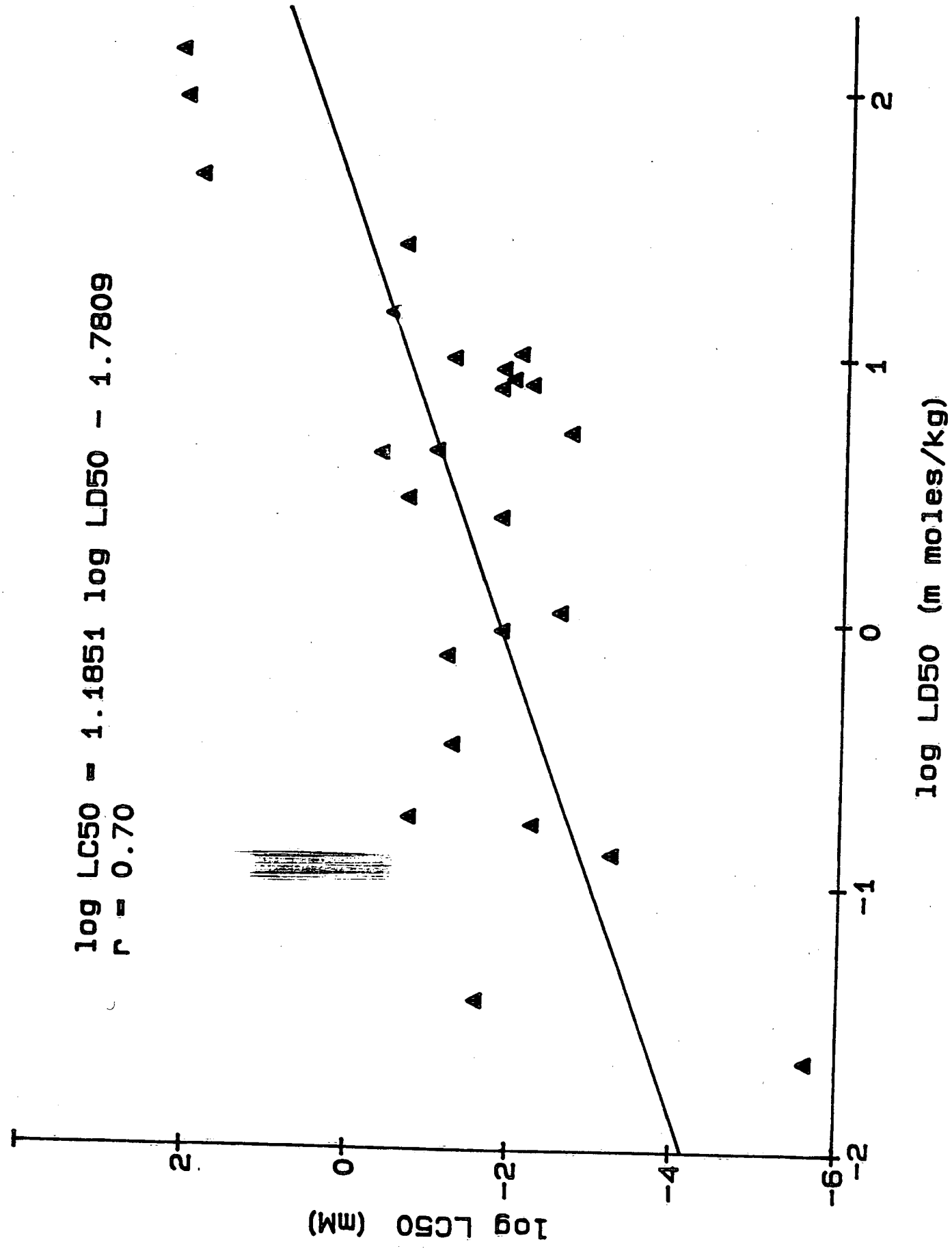
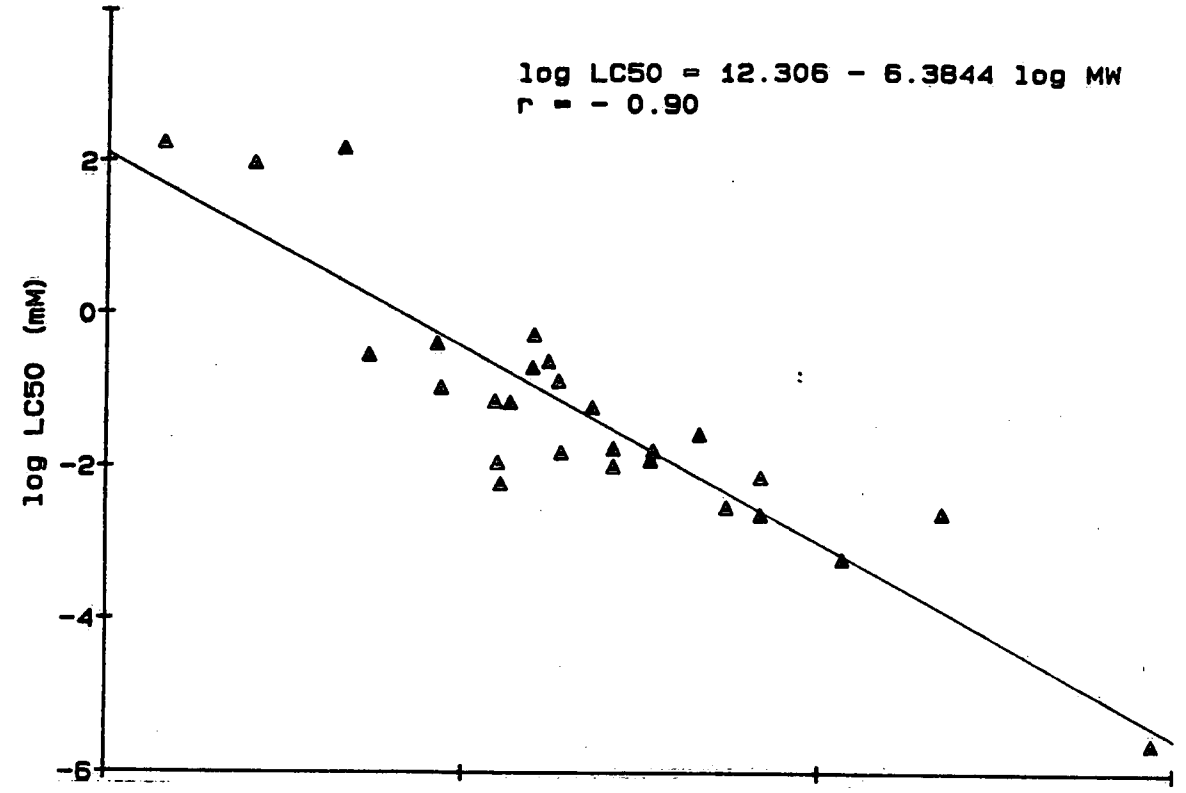

log LC50 = 1.1851 log LD50 - 1.7809
r = 0.70
log LC50 (mM)
log LD50 (m moles/kg)
2
0
-2
-4
-6
2
1
0
-1
-2

Fig 2


log LC50 = 12.306 - 6.3844 log MW
r = - 0.90
log LC50 (mM)
2
0
-2
-4
-6

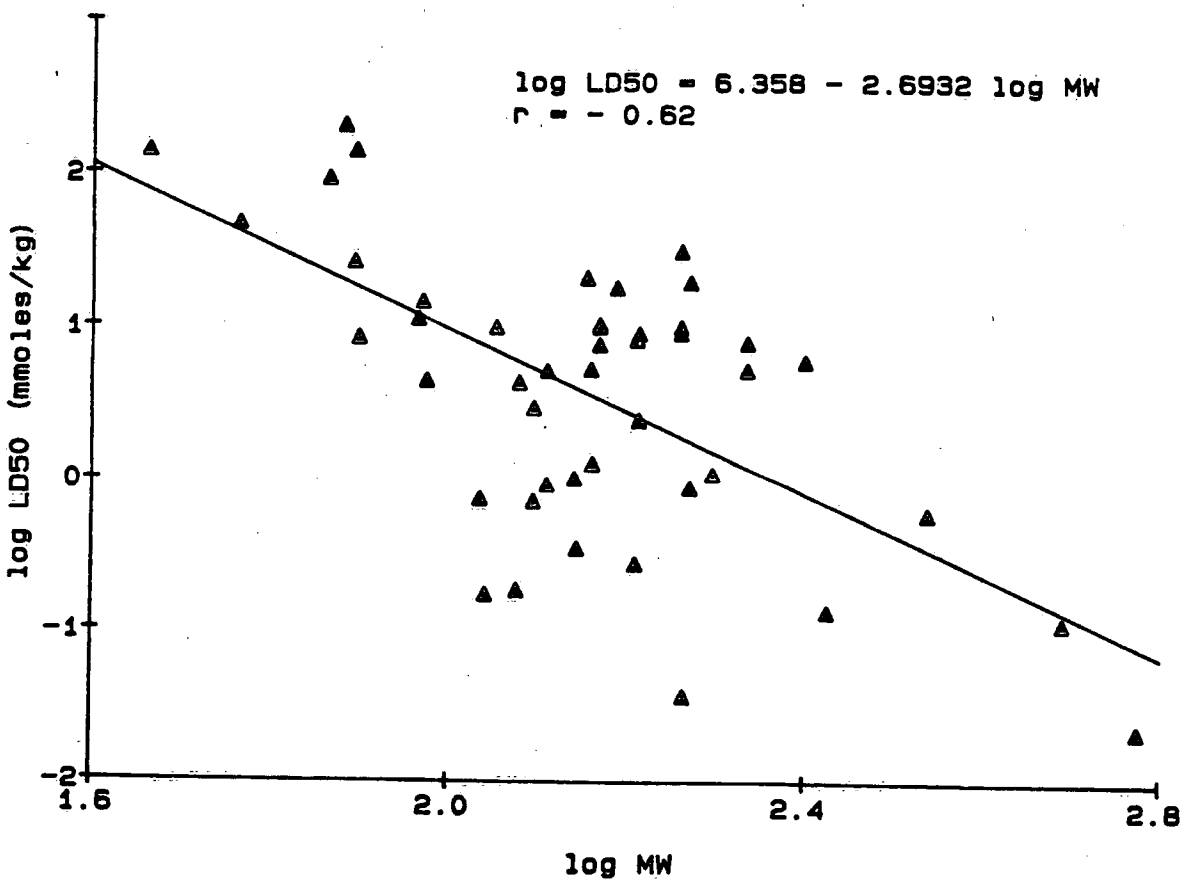
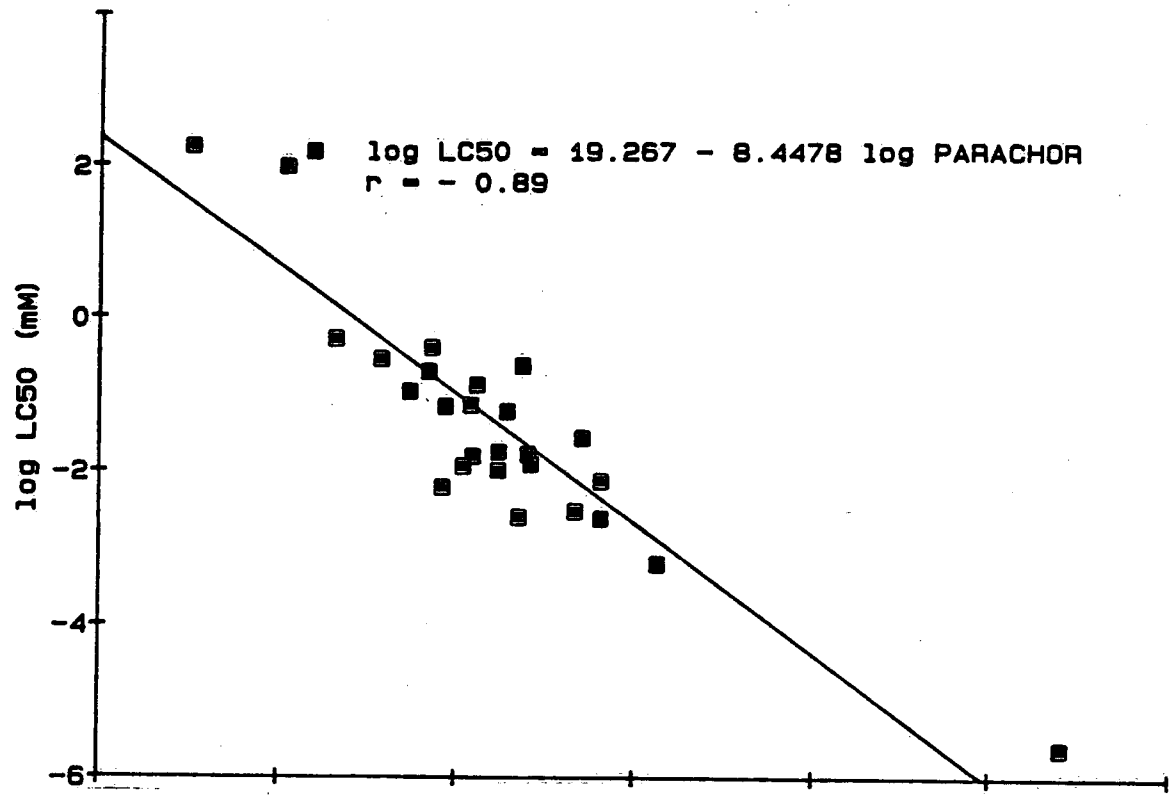

log LD50 = 6.358 - 2.6932 log MW
r = - 0.62
log LD50 (mmoles/kg)
2
1
0
-1
-2
1.6
2.0
2.4
2.8
log MW

Fig 3


log LC50 = 19.267 - 8.4478 log PARACHOR
r = - 0.89
log LC50 (mM)
2
0
-2
-4
-6

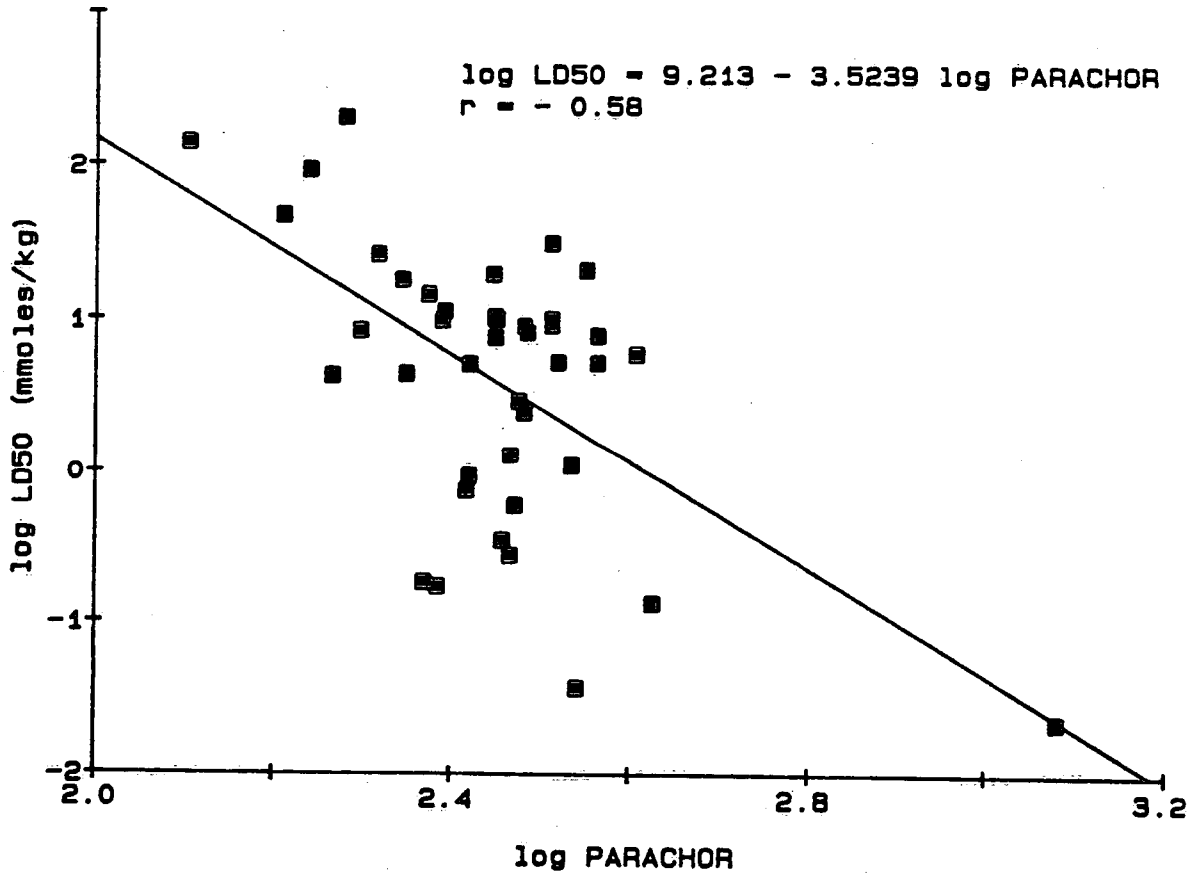
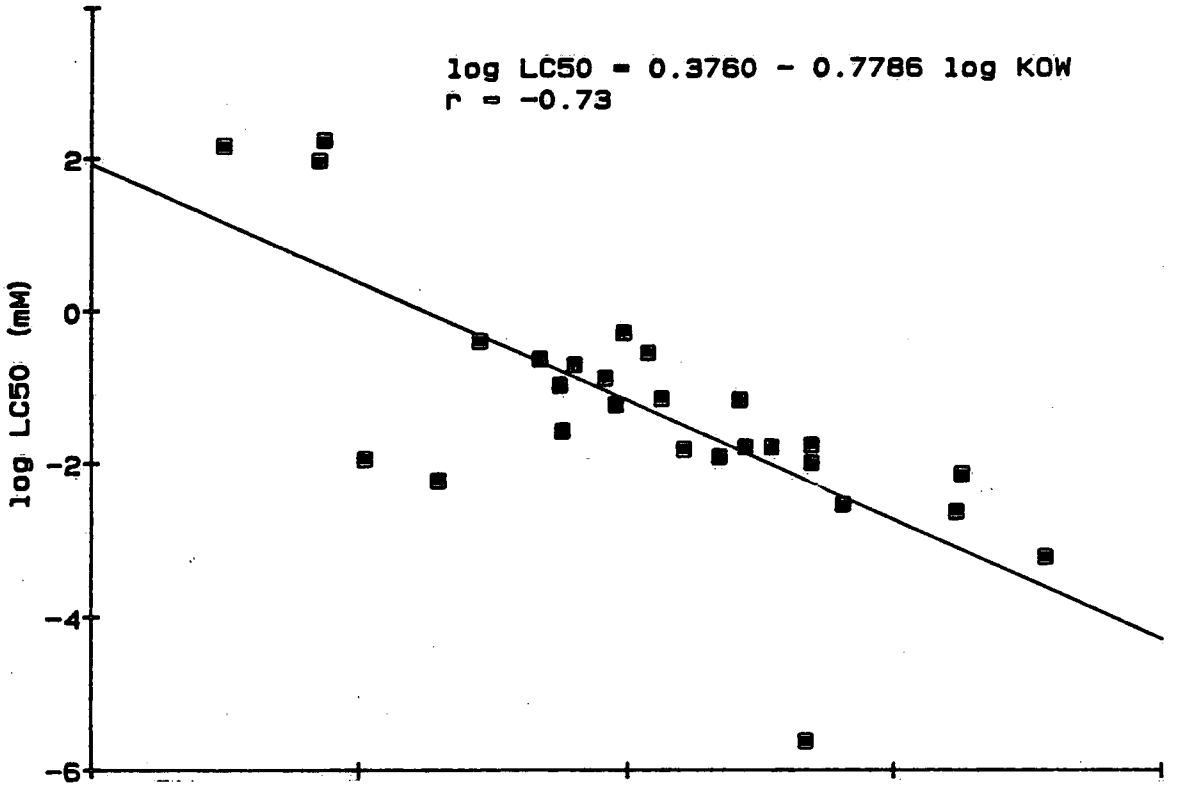
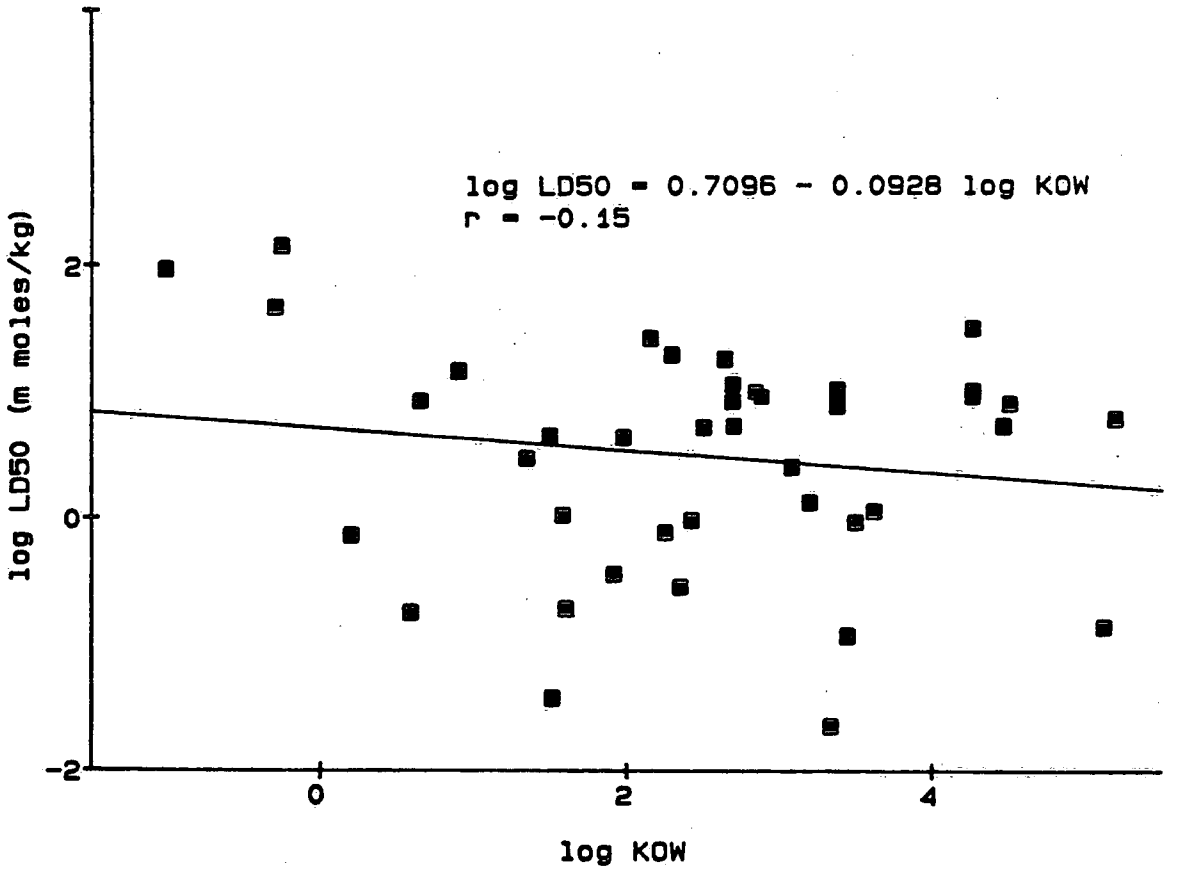

log LD50 = 9.213 - 3.5239 log PARACHOR
r = - 0.58
log LD50 (mmoles/kg)
2
1
0
-1
-2
2.0
2.4
2.8
3.2
log PARACHOR

Fig 4


log LC50 = 0.3760 - 0.7786 log KOW
r = -0.73
log LC50 (mM)
2
0
-2
-4
-6


log LD50 = 0.7096 - 0.0928 log KOW
r = -0.15
log LD50 (m moles/kg)
2
0
-2
0
2
4
log KOW

$$\log LC50 = -0.1014 - 0.6846 \log KOW + 0.8315 \log LD50$$

$r = 0.92$

$N = 25$

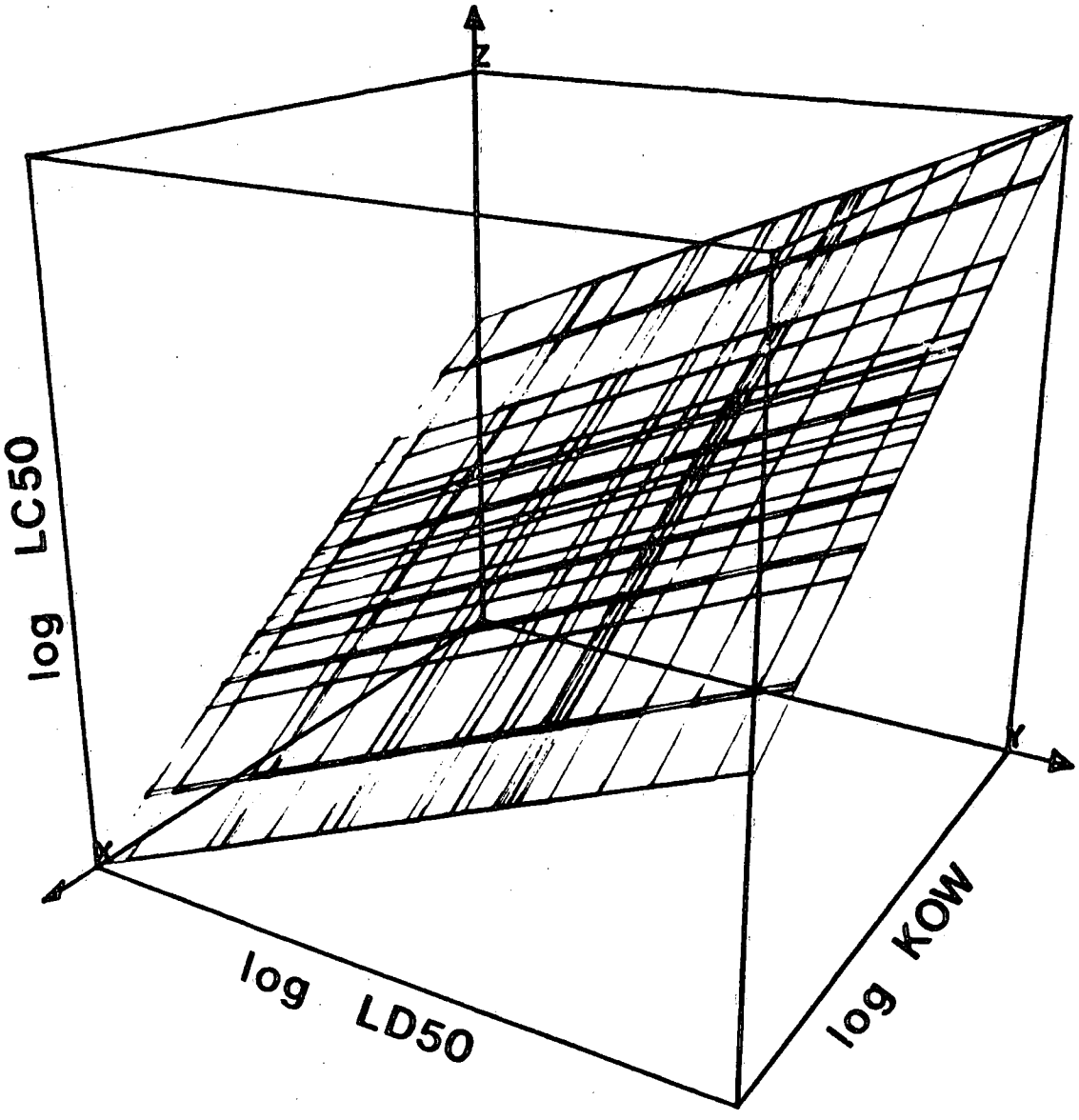


Fig 3

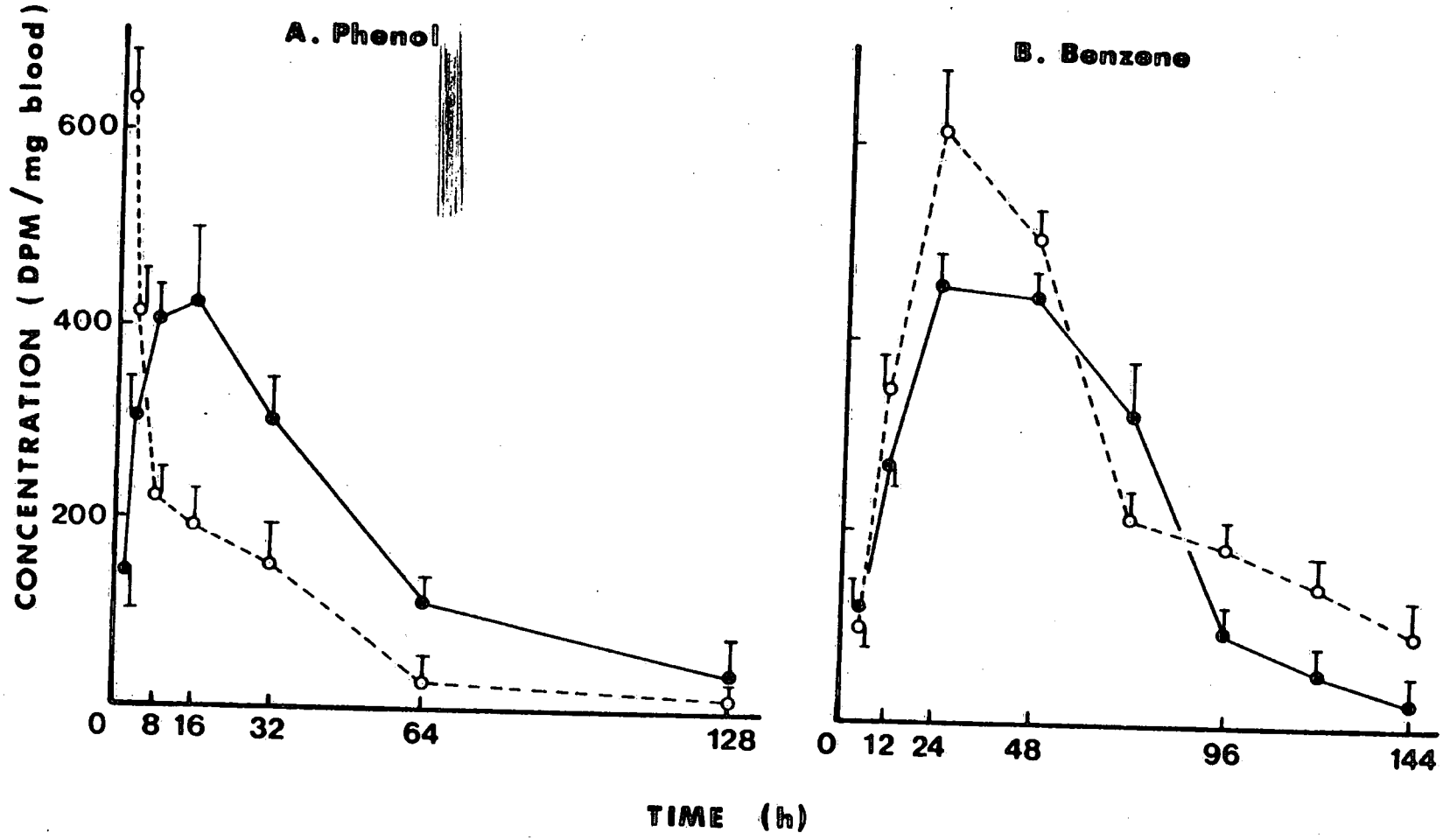

A. Phenol
B. Benzene
CONCENTRATION (DPM / mg blood)
600
400
200
0
8
16
32
64
128
0
12
24
48
96
144
TIME (h)

Fig 2