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INTER-SPECIES ACUTE TOXICITY CORRELATIONS OF 267 CHEMICALS

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MANAGEMENT PERSPECTIVE

Title: Inter-species acute toxicity correlations of 267 chemicals

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Perspective:

This paper represents the results of an extensive data accumulation and analysis with various statistical means, including linear regression, cluster and principal components analyses on a set of 267 individual chemicals. Some of these chemicals are frequently observed environmental contaminants, such as chlorobenzenes and chlorophenols, others are compounds known to be manufactured or used in larger quantities or compounds of particular interest because of their chemical structure. The basis for selection of these chemicals was strictly the availability of published toxicity data (other than the Microtox test data which are measured in-house). Therefore, this data set is thought to represent the most complete collection of such data at this time. The data are acute lethal concentrations to two freshwater fishes, the fathead minnow (Pimephales promelas) and the goldorfe (Leuciscus idus melanotus), the zooplankter Daphnia magna, the ciliate Tetrahymena pyriformis, the algae Scenedesmus quadricauda, the Microtox™ test, which uses the marine bacterium Photobacterium phosphoreum, the acute lethal oral dose to the terrestrial Norway rat and the bulk physico-chemical characteristic known as octanol/water partition coefficient.

The results indicate highly significant correlations between the fathead minnow, goldorfe, Daphnia and Photobacterium concentrations. The cluster and principal component analyses did not detect any clearly defined groups of compounds. The toxicities were also highly collinear with the octanol/water partition coefficients for all species, except the rat.

This work demonstrates:

(i) the usefulness of the comparatively quick and inexpensive Microtox (Photobacterium) test for the determination of the acute toxicity of chemicals to important aquatic species;

(ii) the usefulness of quantitative structure-activity (toxicity) relationships in environmental chemistry and biology.

(iii) that, at present, the effects of too few chemicals have been measured with a standard set of tests. Therefore, there is a need measure the toxic effects of a larger group of representative chemicals (previously estimated to be in the order of one to two thousand) with such a standard set of tests. There is also a need to develop such a standard set of test chemicals which should be representative of all major types, structures and functional groups.

PERSPECTIVE-GESTION

Cet article présente les résultats de l'accumulation d'une foule de donnée et d'analyses au moyen de divers outils statistiques, dont la régression linéaire, les analyses de grappes et en composantes principales, sur 267 produits chimiques différents. Certains de ces produits chimiques sont des contaminants que l'on observe souvent dans l'environnement, tels les chlorobenzènes et les chlorophénols, d'autres sont des composés fabriqués ou utilisés en plus grande quantité que les autres ou des composés présentant un intérêt particulier à cause de leur structure chimique. Le seul critère qui a présidé au choix de ces produits chimiques était la possibilité de trouver des données de toxicité déjà publiées (autres que celles du test Microtox obtenues dans nos laboratoires). Par conséquent, on estime que cet ensemble de données représente la collection la plus complète de données de ce genre à l'heure actuelle. Les donnée sont les concentrations létales aiguës pour deux poissons, la tête-de-boule (Pimephales promelas) et l'ide mélanote (Leuciscus idus melanotus), le zooplancton Daphnia magna, le cilié Tetrahymena pyriformis, l'algue Scenedesmus quadricauda; les résultats du test Microtox™, lequel fait

appel à la bactérie marine Photobacterium phosphoreum; la dose létale aiguë par voie orale pour une espèce terrestre, le rat de Norvège; et la propriété physico-chimique de masse appelée coefficient de partage octanol/eau.

Les résultats indiquent qu'il y a une corrélation très significative entre les concentrations pour la tête-de-boule, l'ide mélanote, Daphnia et Photobacterium. Les analyses de grappes et en composantes principales ne nous ont pas permis de déceler des groupes de composés bien définis. Les valeurs de toxicité présentaient également une corrélation très élevée avec les coefficients de partage octanol/eau pour toutes les espèces, sauf le rat.

Ce travail démontre :

i) l'utilité du test Microtox (Photobacterium), rapide et peu coûteux comparé à d'autres tests servant à déterminer la toxicité aiguë des produits chimiques pour les espèces aquatiques importantes;

ii) l'utilité des relations quantitatives entre la

structure et l'activité (toxicité) en chimie et en biologie environnementales.

iii) que, jusqu'à présent, trop peu de produits chimiques ont fait l'objet de mesures dans un système normalisé de tests. Par conséquent, il faut mesurer les effets toxiques d'un groupe plus important de produits chimiques représentatifs (qu'on a déjà estimés être de l'ordre d'un à deux milles) à l'aide d'un tel ensemble normalisé de tests. Il faut également mettre au point un ensemble normalisé de produits chimiques qui pourraient être utilisés dans ces tests et qui devraient être représentatifs de tous les principaux types, structures et groupements fonctionnels.

RÉSUMÉ

Les valeurs de toxicité aiguë de 267 composés pour six espèces aquatiques et une espèce terrestre ont été étudiées au moyen de techniques de corrélation, d'analyse en composantes principales et d'analyse de grappes pour déterminer les relations entre elles et avec le coefficient de partage octanol/eau des composés. Le critère qui a présidé au choix des produits chimiques a été la possibilité de mesurer au moins trois des paramètres suivants : les concentrations létales aiguës (24 h à 96 h) (LC50) pour les poissons tête-de-boule (Pimephales promelas) et ide mélanote (Leuciscus idus melanotus), le zooplancton Daphnia magna, le cilié Tetrahymena pyriformis, l'algue Scenedesmus quadricauda; les concentrations inhibitrices (30 min) (EC50) pour la bactérie marine luminescente Photobacterium phosphoreum (le test Microtox™), la dose aiguë par voie orale (LD50) pour le rat de Norvège commun et le coefficient de partage octanol/eau (log P ou log K_{ow}).

Les résultats indiquent des corrélations très significatives entre la LC50 mesurée chez la tête-de-boule, l'ide mélanote et Daphnia et la EC50 chez Photobacterium. Les analyses de

grappes et en composantes principales n'ont pas permis de déceler des groupes de composés bien définis. Les valeurs de toxicité présentaient également une colinéarité élevée avec les coefficients de partage octanol/eau pour toutes les espèces sauf le rat, où deux relations sont indiquées, avec la division à log P=2.00.

INTER-SPECIES ACUTE TOXICITY CORRELATIONS OF 267 CHEMICALS

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ABSTRACT

The acute toxicities of 267 compounds for six aquatic and one terrestrial species were investigated with correlation, principal component and cluster analysis techniques for relationships with each other and with the compounds' octanol/water partition coefficient. Selection of the investigated chemicals was based on the availability of at least three of the following measured parameters: Acute (24-hr to 96-hr) lethal concentrations (LC50) to the fish fathead minnow (*Pimephales promelas*), the fish goldorfe (*Leuciscus idus melanotus*), the zooplankter *Daphnia magna*, the ciliate *Tetrahymena pyriformis*, the algae *Scenedesmus quadricauda*, the (30-min) inhibitory concentrations (EC50) to the luminescent marine bacterium *Photobacterium phosphoreum* (the Microtox™ test), the acute oral dose (LD50) for the common Norway rat and the octanol/water partition coefficient (log P or log K_{ow}).

The results indicate highly significant correlations between the fathead minnow, goldorfe and *Daphnia* LC50 and the *Photobacterium* EC50 concentrations. The cluster and principal components analyses did not detect any clearly defined groups of compounds. The toxicities were also highly collinear with the octanol/water partition coefficients for all species except the rat, where two relationships are indicated, with the division at log P= 2.00.

INTRODUCTION

The steadily increasing wealth of acute and semi-chronic toxicity data of single chemicals to various aquatic and terrestrial species has stimulated interest in both intra- and interspecies comparisons and relationships of such effects. Because of the importance of the aquatic system as vehicle for the transport, transformation and biological uptake of many hazardous chemicals, toxicities of chemicals to important and representative aquatic species are measured in laboratories worldwide. Among the most frequently used species are fish, including the fathead minnow, goldorfe, rainbow trout and zebrafish, zooplankton such as *Daphnia* sp., various algae such as *Scenedesmus* sp. and, more recently, the marine bacterium *Photobacterium phosphoreum*, commonly known as the Microtox™ [1] test. For fish, flow-through tests are preferable and standard exposure times are in the 24-hr to 96-hr range for acute lethal concentration determinations to one-half of the population (LC50). This type of work usually requires a considerable amount of chemical and also an extensive experimental control as well as considerable experience and cost in growing, acclimatizing and keeping the test species stocks. In

[1] Microtox is a trademark of Microbics Corp., Carlsbad, California, USA.

contrast, static tests, as normally used with the much smaller zooplankton, ciliate or algae species, require less effort and material cost. Even more cost-efficient appear the new bacterial bioassays, such as the Microtox™ test. On average, less than 100 mg of substance suffice to undertake several replicate tests and the results can be known in minutes or a few hours. The bacteria required can also be purchased from commercial suppliers and can be stored for several months without significant loss of viability. Given these advantages, it is of considerable interest to compare the results of the various bioassays and to determine their sensitivity relative to each other and to systematic changes in the molecular structure of the toxicants.

With the objective of investigating relationships among the toxicity test methods, the possibility of finding groups of compounds which are similar to each other on the basis of some or all of the parameters and the pairwise relationships between parameters were considered. The methods used were cluster and principal component analysis in the first case and regression analysis in the latter. The number of possible combinations of parameters that could be used in any analysis is limited due to the incomplete set of measurements for all but two of the compounds, and only some of the possible combinations have been analyzed.

DATA AND METHODS

Toxicity Data

The toxicity data were mostly obtained from the literature. Specifically, flow-through fathead minnow (FHM) 96-hr LC50 values were obtained from Brooke et al. (1984) and Geiger et al. (1985, 1986, 1988), the static goldorfen (GO) 48-hr LC50 values from Juhnke and Ludemann (1978), the static green algae (BA) data from Bringmann and Kuhn (1980), the static *Tetrahymena pyriformis* (TEHY) 48-hr (in some cases 60-hr) LC50 values from Schultz and coworkers (Schultz et al., 1989), the rat 96-hr lethal dose (LD50) values from RTECS (1987), (in a few cases, where other route of administration rat and mouse data and no oral LD50 rat but such mouse data were available, the latter were used), the static *Daphnia magna* (DM) 24-hr LC50 values from several sources including Devillers (1988) and LeBlanc (1980), and the 30-min Microtox (MTOX) values from Kaiser and Ribo (1988) and unpublished results of this laboratory. The octanol/water partition coefficients (log K_{ow} or log P) data were taken from Hansch and Leo (1979) or, in a few cases, were computed from the values for closely related compounds and π values for the relevant substituents.

For the selection of compounds from the data base, the following criterion was applied: At least three measured values of the eight toxicity and physical properties had to be available. This selection resulted in 267 compounds from a variety of chemical classes including aliphatic, aromatic and five- and six-ring nitrogen heterocyclic compounds, with many different substituents and/or functional groups, including nitro, amino, hydroxy, cyano, keto (aldehyde and ketone), chloro, bromo and fluoro groups. A complete listing of the compounds, their toxicity and log P values and their Chemical Abstract Service accession numbers is found in Table 1, which is available, on request, from the authors. Also given in Table 1 are the indicator values for several functional groups which indicate the absence (0) or presence of one (1) to three (3) of each of the groups.–All toxicity values are converted to the negative logarithm of the millimolar concentrations.

Abbreviations

MTOX	Microtox™ test (*Photobacterium phosphoreum*), 30-min EC50, static;
FHM	Fathead minnow (*Pimephales promelas*), 96-hr LC50, flow-through;
GO	Goldorfe (*Leuciscus idus melanotus*), 48-hr LC50, static;
DM	crustacean (*Daphnia magna*), 24-hr LC50, static;
BA	blue alga (*Scenedesmus quadricauda*), 24-hr LC50, static;
TEHY	ciliate (*Tetrahymena pyriformis*), 48-hr to 60-hr LC50, static;
RAT	Norway rat, 96-hr single oral dose LD50.

Specifics of Data Set

The total number (n) of compounds measured for each parameter is given as follows:

Parameter	MTOX	FHM	GO	DM	TEHY	RAT	BA	log P
n	249	145	66	108	114	160	56	260

Although measurements were available for at least three parameters for all of the 267 compounds in the data set, the numbers of compounds with measurements on the same three or more parameters was much lower (Table 2). There is a further reduction in the number of compounds available when they are classified by functional group. For example, of the 242 compounds with both MTOX and log P measurements, the distribution of compounds which possess a phenol is given in Table 3.

In terms of the ascribed functional groups, certain simplifications were applied in order to limit the number of functional group parameters. For this reason, aldehydes and ketones are included in the keto group and carboxy acids were grouped as containing both a keto and alcohol group. Aromatic compounds with ring-carbon bonds to either chlorine, bromine or iodine were treated identically and are differentiated only by the number of such bonds in each compound. N-5 and N-6, respectively, are indicators of the number of nitrogen containing five- and six-membered rings, respectively in each compound.

Statistical Methods and Grouping

The data matrix was investigated with linear regression, cluster and principal component analysis in an interactive APL language environment using the authors' programs. The component scores of the principal components obtained from the variance-covariance matrix of the parameters were plotted pairwise and the plots inspected for groups of compounds which were separate from other compounds. The clusters were determined by a non-hierarchical nearest centroid k means procedure (Anderberg, 1973). The number of clusters chosen (five), is the best compromise between graphical cluster separation and the proportion of the total variation accounted for by the clusters, calculated as a ratio of the sums of squares.

The five parameter data subset with the largest number of compounds is the set consisting of 59 compounds with the measurements for MTOX, FHM, DM, RAT and log P. For comparison, a larger set consisting of 127 compounds with MTOX, FHM and log P, and three sets with fewer parameters measured, namely (i) only FHM and DM in the above noted 59-compound set, (ii) FHM and DM for all 73 compounds for which both parameters were measured, and (iii) the 32 compounds with FHM, GO and DM values measured were also analyzed. As the general conclusions were similar, only the results for the five-parameter, 59-compound set are given here.

Regression analysis assuming a polynomial form of degree one or more was used, with various extensions to test for equality of relationships. A procedure for estimating the point of change in a regression relationship was also used (Esterby and El-Shaarawi, 1981).

RESULTS

Cluster Analysis

Cluster analysis and the graphical methods which display the data points in a low dimensional space are useful in identifying groups of objects which are similar to each other, but dissimilar to objects in other groups. Here, the objective is to find groups of compounds where the compounds within a group have similar parameter values. For this grouping to be useful, ultimately, it should uncover some structure(s) in the data set which will suggest a means of predicting toxicity as measured for one or more species from another species or on the basis of the nature of the compound. Such groups should also possess stability, i.e. should be unaffected by the addition of new compounds to the data set. They should also either be separated from other groups or have a feature common to all compounds in a group, not also present in other groups, which would aid prediction, e.g., the presence of a particular functional group.

Pairwise plots of the 59 compounds show that all parameters have monotonic relationships, increasing together over the range of observation, with the exception of the pairs, which include RAT, for which such a simple relationship does not hold. Five clusters, accounting for 76% of the total variation in this data set, divide the range of each variable into groups with increasing means but not necessarily non-overlapping ranges (Fig. 1). Cluster analysis based on only FHM and DM (73 compounds) accounts for 87% of the total variation and provide five non-overlapping clusters, however, cluster membership is not stable when going from the 59 compounds to the set of 73. Thus, although these clusters account for a reasonable amount of variation, they are neither stable nor separated from each other.

The presence/absence of functional groups was not used in the cluster analysis since it would not only reduce the available numbers of compounds further, but would also introduce the problem of how to combine measures of similarity or distance for variables of different type. It thus seemed more reasonable to perform the cluster analysis on the toxicity measurements and log P, and then to graphically identify compounds with common functional groups. Since intramolecular interaction between functional groups are known to affect toxicity (Kaiser and Gough, 1988), compounds with functional groups of more than one type have been identified only when in numbers large enough for further analysis.

The alcohols span most of the log P range and appear in four of the five clusters, as do the keto compounds. The only group of compounds restricted to one cluster are the compounds with one phenol group, however, this cluster (cluster 3) also contains compounds with three of the other identified functional groups. Thus, the clusters do not contain unique functional groups as the compounds containing a particular functional group span a considerable portion of the log P range.

Principal Component Analysis

The first two principal components (PC1, PC2) account for 90% of the variance (Table 4) and reflect the pairwise correlation (Table 5). The plots of the compounds on the first two components, suggest a group of compounds with scores on PC1 greater than 0 and another group with scores less than 0, where the scatter is greater along the PC2 axis in the former and along the PC1 axis in the latter. Two compounds are separated at the top of the plot. However, when the functional groups are identified, again as above, the compounds with different functional groups intermingle (Fig. 2). The reduced dimensional plot is dividing the range of the original variables, although at a larger interval, as did the cluster analysis (Fig. 1). This can be seen by identifying the clusters to which compounds were assigned in the cluster analysis on plots of PC1 versus PC2 (Fig. 3).

Regression Analysis

Since the parameters, with the exception of RAT, increase together, methods for identifying factors which alter the relationships between variables should be more useful than the conventional grouping methods, examples of which were used above. As a first look at this, relationships within various combinations of parameters, sometimes with functional groups identified, have been examined by regression and related methods. To obtain larger numbers of compounds, subsets with fewer than the five parameters used in the previous methods were chosen. The analysis here is also of an exploratory nature, attempting to discover structure in the data and thus, results are simply what has been identified thus far.

The largest subset of data available for pairwise relationships is the set of 242 compounds with MTOX and log P measurements with the features of a dense band of points, the extension of which in the lower MTOX values, suggests curvature of the relationship and above which are a few scattered compounds with higher MTOX values for the corresponding log P value. A linear relationship fit to all of these data clearly suffers from lack of fit and explains only 46% of the variation. The identification of compounds with specific functional groups (Fig. 4) suggests that compounds with different functional groups may have different relationships between MTOX and log P and show that some of the higher MTOX values are atypical of the remainder of compounds with the same functional group present. The difference in the relationship for the sets of compounds where either one phenol or one pyridine (nitrogen containing six-membered ring) or no functional groups are present, is primarily in the slope of the line. For the set of compounds with one keto group, log P is not a good predictor of MTOX. The presence of two or more aromatic chloro substituents when one phenol group is present significantly alters the relationship between MTOX and log P ($p<0.01$) relative to that when fewer than two aromatic chloro groups are present with one phenol group.

For the set of compounds with one keto group, log P is not a good predictor of MTOX. The presence of two or more aromatic chloro substituents when one phenol group is present significantly alters the relationship between MTOX and log P ($p<0.01$) relative to that when fewer than two aromatic chloro groups are present with one phenol group. In fact, at the $p=0.03$ level, for the latter compounds, MTOX is significantly higher than for the former compounds, over the common range of log P observed here.

A relationship between MTOX and log P very different was found for the simple carboxy (alcohol+keto) series. The increase in unit of MTOX per unit change in log P is much greater and the residual variation is very small. Similarly, precisely determined linear relationships between each of FHM, GO, DM, BA with log P were found with r^2 values of 0.984 (n= 17), 0.979 (n= 11), 0.949 (n= 12) and 0.927 (n= 11), respectively. The increase in toxicity with increasing number of carbons in the chain is shown in Fig. 5; excluding c-hexanone, butan-2-ol and propan-2-ol, the correlation coefficient is $r^2= 0.985$. This series of alcohols and ketones are part of a set of 127 compounds for which measurements are available for MTOX, FHM and log P. Although there is considerably more scatter for MTOX, this series tends to form a lower border for the band of points in the plots of FHM versus log P and MTOX versus log P (Fig. 6), which has long been recognized as the narcosis cutoff (Lipnick, 1989).

The prediction of toxicity from toxicity measurements in organisms of lower order and log P was considered for the 127 compounds with MTOX, FHM and log P values and the 93 compounds with MTOX, FHM, RAT and log P data. For the former set, linear relationships with FHM as the dependent variable were fitted by regression. Log P alone adequately accounted for the variation in FHM for compounds with either one phenol group only or none of the identified functional groups present, but in keeping with the observation made above, log P was a poorer predictor variable than MTOX for compounds with 1 keto group (Table 6). When functional groups not identified, both log P and MTOX were needed as predictor variables.

Plots of the 93 compounds with MTOX, FHM, RAT and log P measured suggest that non-linearity exists in the relationships between RAT and log P and RAT and MTOX. A segmented regression between RAT and log P (Fig. 7) explains nearly as much of the variation in RAT toxicity as the regression with MTOX, FHM and log P (Table 7). Since the relationship between RAT and FHM is more linear, FHM also explains nearly as much. It should be noted that the point at which the relationship between RAT and log P changes, was determined from the rat and log P data by a method which seeks the point which minimizes the residual variation from both lines.

DISCUSSION

Recent work on quantitative structure-toxicity relationships of environmental contaminants has resulted in various models for intraspecies (Hodson et al., 1988) and interspecies toxicity correlations (Enslein et al., 1987; Janardan et al., 1984; Lipnick, 1989; Slooff et al., 1983; Thurston et al., 1985; Wellens, 1982) as well as in the recognition of species-specific effects of certain groups of chemicals and the possibility of broad generalisations for the biological activity of other types of chemicals (Hansch et al., 1989). The objective here, with the large multi-species data set, was to identify groups of compounds of characteristics of compounds useful for the prediction of toxic effects from one species to another.

The present results suggest that the generally available cluster analysis and low-dimensional graphical techniques are not useful for this purpose as they attempt to identify groups with approximately constant parameter values within a group. In view of this, the particular choice of clustering algorithm should not be responsible for the lack of success and this was verified by using several versions of hierarchical methods and similarity measures. Although, as noted above, only some of the possible data subsets and functional groups have been considered, these conclusions should be more generally valid. Methods which account for the features of the data displayed in plots, namely linear relationships between parameters and the spanning of a large range of parameter values by compounds of similar nature are required. The correlational studies have taken these features into account and other methods are being investigated.

CONCLUSIONS

This work demonstrates a high degree of collinearity between the MTOX, FHM, TEHY toxicity and octanol/water partition coefficient data over several orders of magnitude. This finding also includes some compounds known to act by specific toxic action mechanisms. A lower collinearity is found for the algae and rat toxicity data. Although there are severe limitations imposed by the incompleteness of the data set, there is no indication to suspect substantial changes in these relationships for a more complete data set. Nevertheless, it appears most desirable to measure the most important toxicity and physico-chemical parameter values for a larger set of compounds. This set should also cover sufficient representatives of each important functional group, alone and in combination with others, and types of chemical structures. A previous recommendation in this regard envisaged such a set to include approximately 1200 compounds (U.S. EPA, 1981). As yet, there does not appear to have been a systematic and concerted follow-up of this recommendation.

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List of Figures

Table 1. Toxicity and log P values of chemicals.

Note: Because of its large size, this table is omitted. However, it may be obtained from the first author upon written request.

Table 2. Distribution of compounds in data set by number and type of toxicity parameter measured.

Number of parameters with measurements	Number of compounds			
	Smallest number		Largest number	
	n	Parameters	n	Parameters
2	7	GO, TEHY	242	MTOX, log P
3	3	FHM, GO, TEHY	138	MTOX, RAT, log P
4	2	FHM, GO, DM, TEHY	93	MTOX, FHM, RAT, log P
5	2	FHM, GO, DM, TEHY, X[a]	59	MTOX, FHM, DM, RAT, logP

[a] All parameters were measured for these two compounds.

Table 3. Distribution of compounds containing the phenol functional group and with measured MTOX and log P values.

Functional groups	Number in set[a]
1 phenol group	55
1 phenol group only	22
1 phenol group and ≤1 aromatic ring Cl	39
1 phenol group and ≥2 aromatic ring Cl	16

[a] Exclusive of outlier 4-ethylphenol.

Table 4. Principal components of the 59 compound subset.

	Standardized Eigenvector				
Parameter	1	2	3	4	5
MTOX	1.00	-0.00	-0.55	-1.00	-0.19
FHM	0.91	-0.20	0.71	0.38	-1.00
DM	0.91	-0.38	-0.84	0.70	0.49
RAT	0.37	-0.59	1.00	-0.29	0.82
log P	0.74	1.00	0.40	0.17	0.47
% variation					
single	78.6	11.6	3.7	3.4	2.7
cumulative	78.6	90.2	93.9	97.3	100.0

Table 5. Correlation matrix.

	MTOX	FHM	DM	RAT	log P
MTOX	1	0.85	0.85	0.57	0.71
FHM		1	0.85	0.64	0.66
DM			1	0.62	0.59
RAT				1	0.23

Table 6. Linear relationships of fathead minnow (FHM), Microtox (MTOX) and octanol/water partition coefficient (log P).

Dependent variable	Predictor variable	Functional group	Number of compounds	r^2
FHM	log P	1 phenol only	15	0.77
FHM	log P	none	9	0.79
FHM	MTOX	1 keto only	11[a,b]	0.58
FHM	log P, MTOX	not identified	126[a]	0.76

[a] Acrolein was excluded.
[b] 2-decanone was excluded because its log P was much higher than others and as a lone point would influence the regression too much.

Table 7. Regression relationships of RAT, FHM, MTOX and log P.

Dependent variable	Predictor variable(s)	Range of of log P	Number of compounds[a]	r^2	Regression Intercept	Slope
RAT	MTOX, FHM, log P	all	91	0.41		
RAT	log P	all	91	0.09	-1.33	0.17
RAT	log P	<2.00	48[b]	0.37	-1.74	0.69
		>2.00	43		-1.88	0.28
RAT	FHM	all	91	0.34	-1.16	0.36

[a] Acrolein and caffeine were excluded because values for RAT were higher than those of other compounds with similar log P.
[b] The sample with log P= 2.00, was determined as the point at which the regression relationship changed.

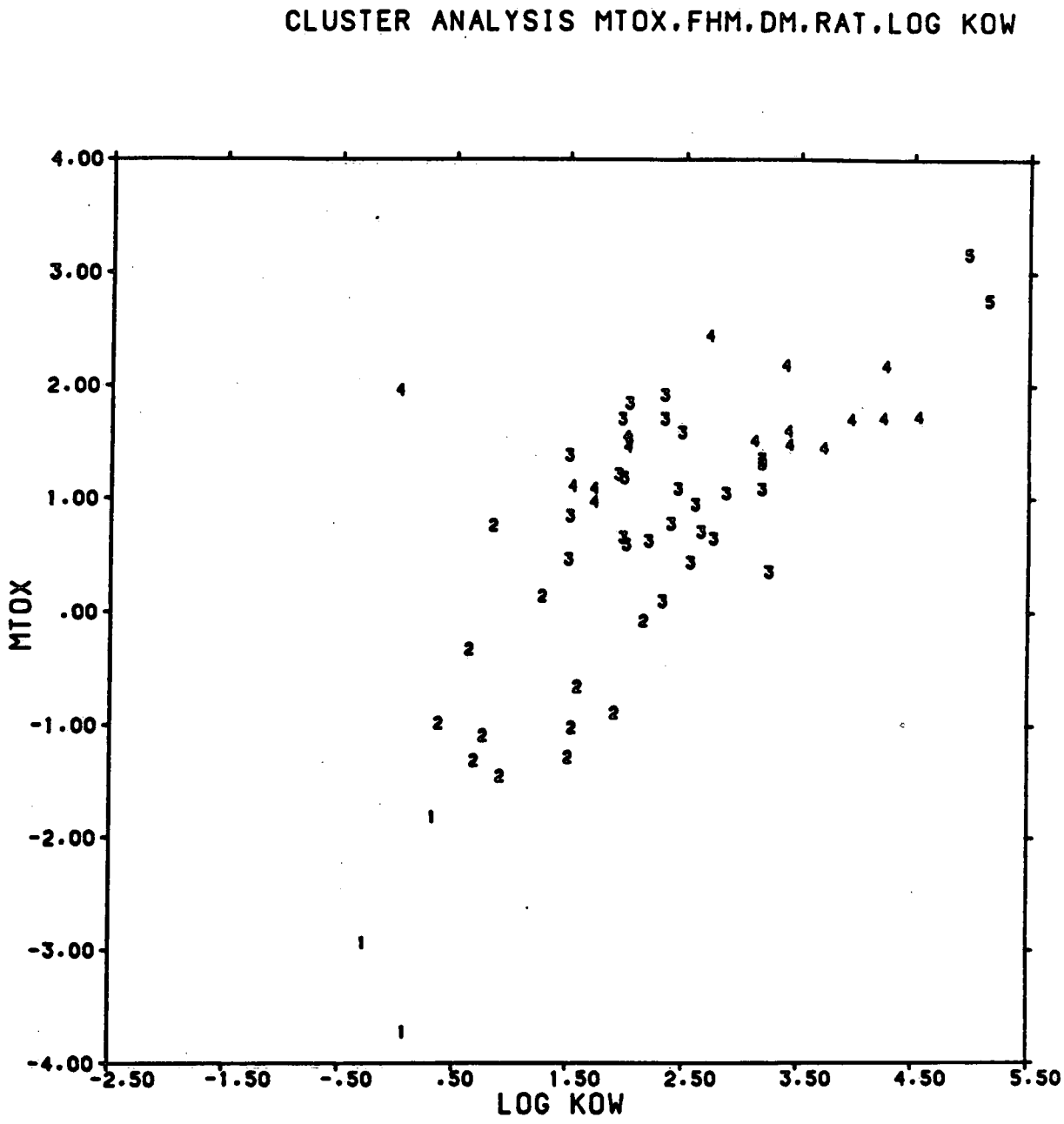

CLUSTER ANALYSIS MTOX.FHM.DM.RAT.LOG KOW
MTOX
LOG KOW
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
-3.00
-4.00
-2.50
-1.50
-.50
.50
1.50
2.50
3.50
4.50
5.50

FIGURE 1

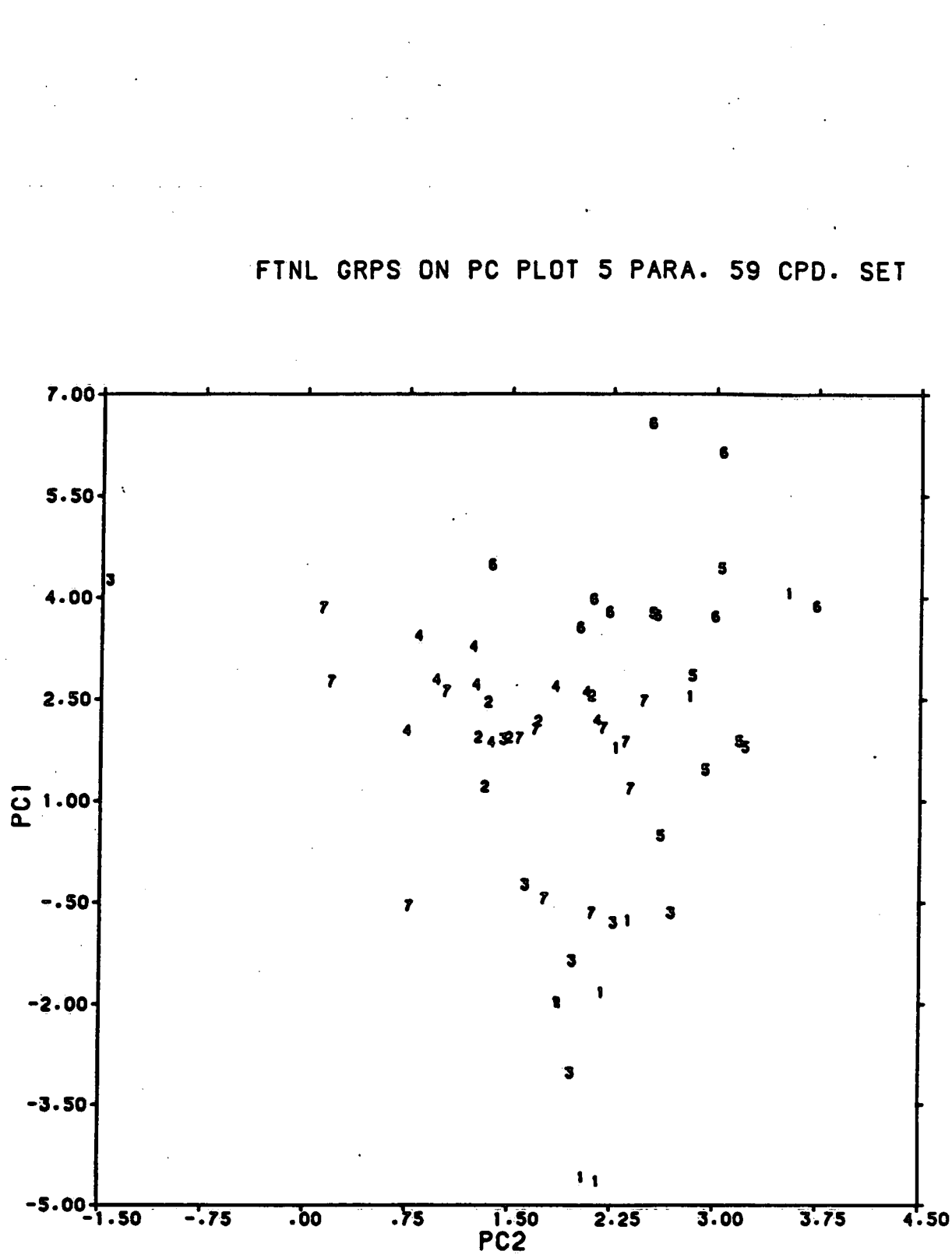

FTNL GRPS ON PC PLOT 5 PARA. 59 CPD. SET
7.00
5.50
4.00
2.50
1.00
-.50
-2.00
-3.50
-5.00
PC1
-1.50
-.75
.00
.75
1.50
2.25
3.00
3.75
4.50
PC2

FIGURE 2

CLUSTERS ON PC PLOT 5 PARA. 59 CPDS

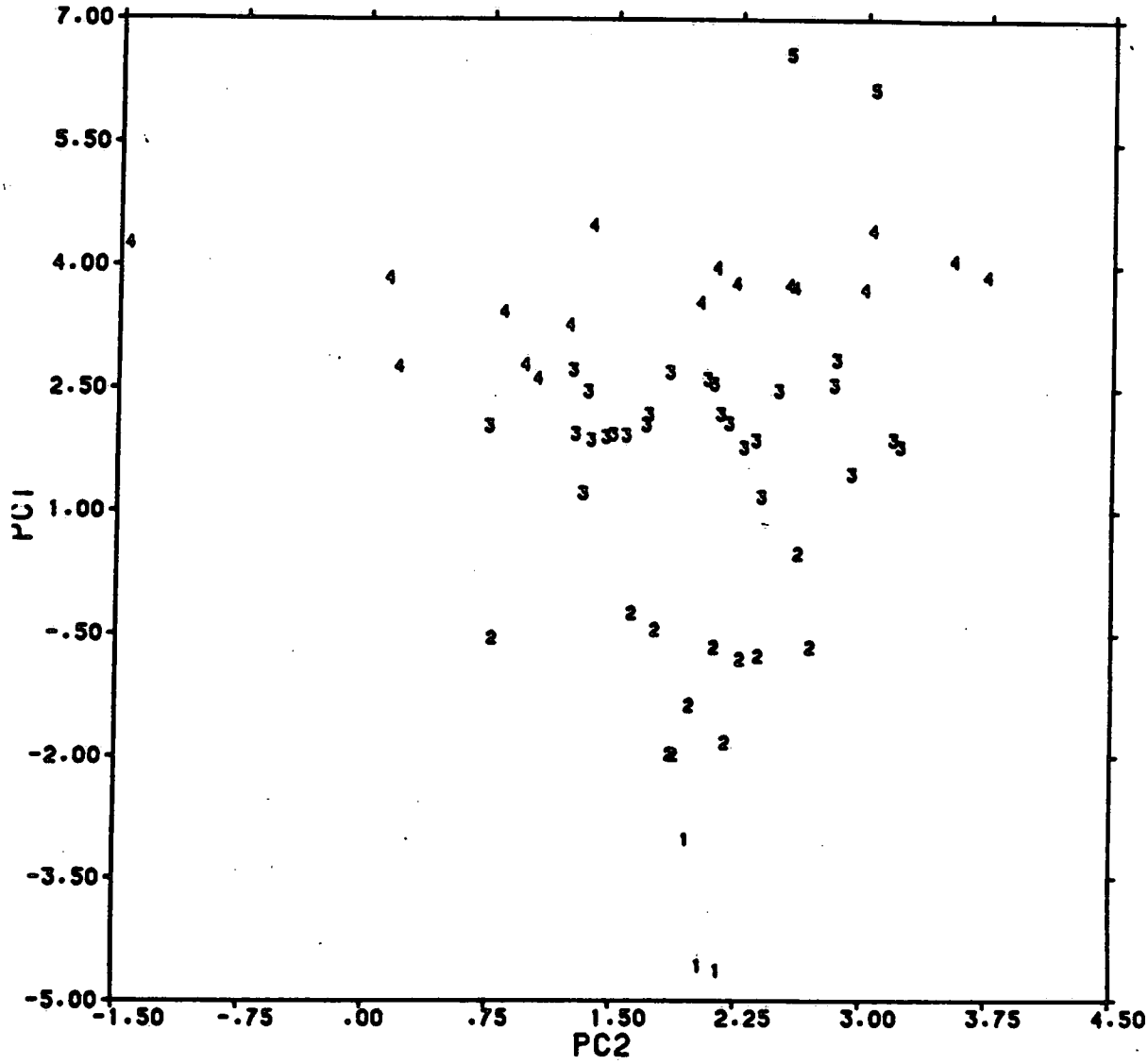


FIGURE 3

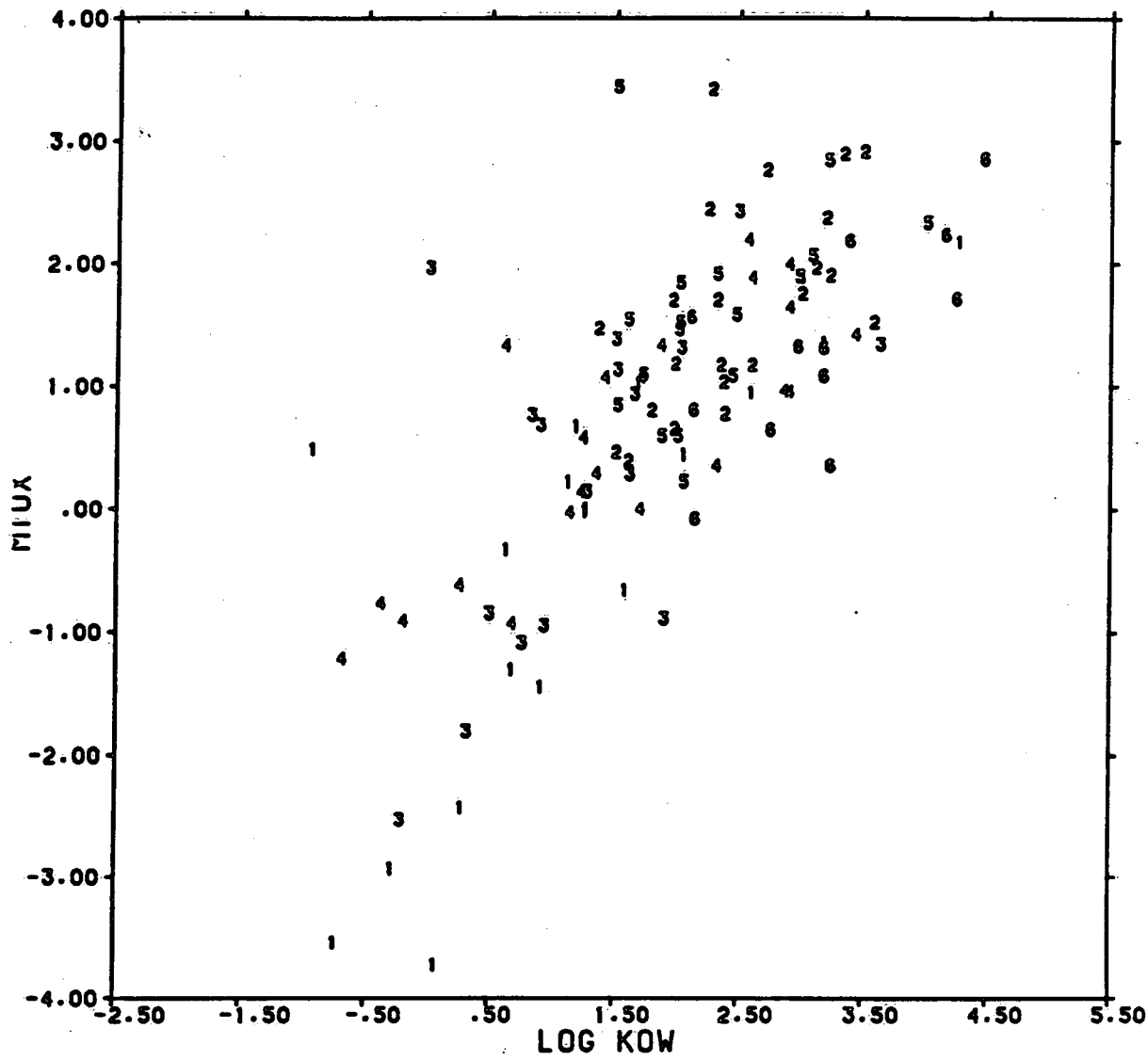

IDENTIFIED FNL GRPS (N=109) MTOX.LOG KOW
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
-3.00
-4.00
MTOX
-2.50
-1.50
-.50
.50
1.50
2.50
3.50
4.50
5.50
LOG KOW

FIGURE 4

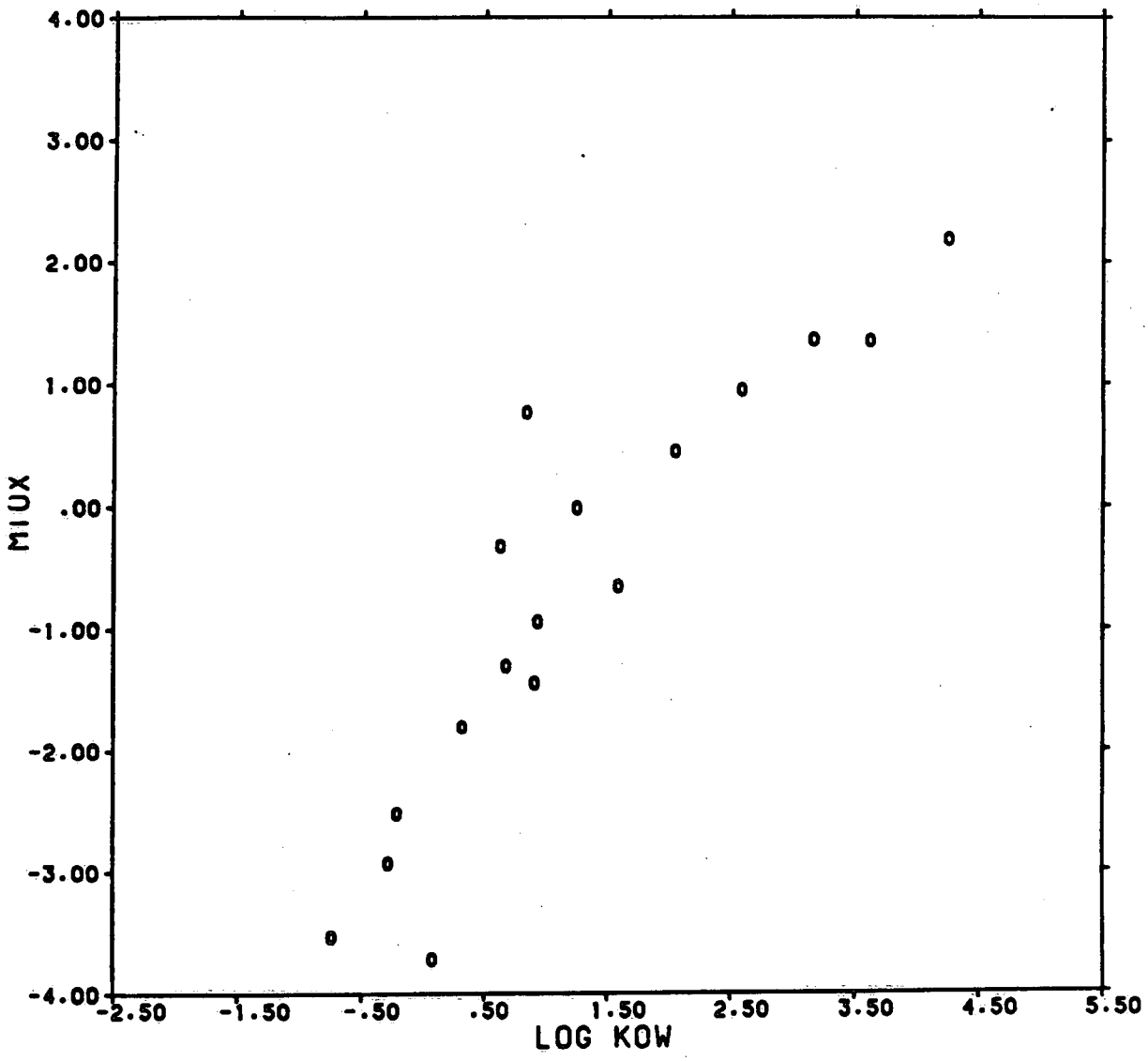

SIMPLE ALCOHOL KETONE SERIES
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
-3.00
-4.00
MIUX
-2.50
-1.50
-.50
.50
1.50
2.50
3.50
4.50
5.50
LOG KOW

FIGURE 5

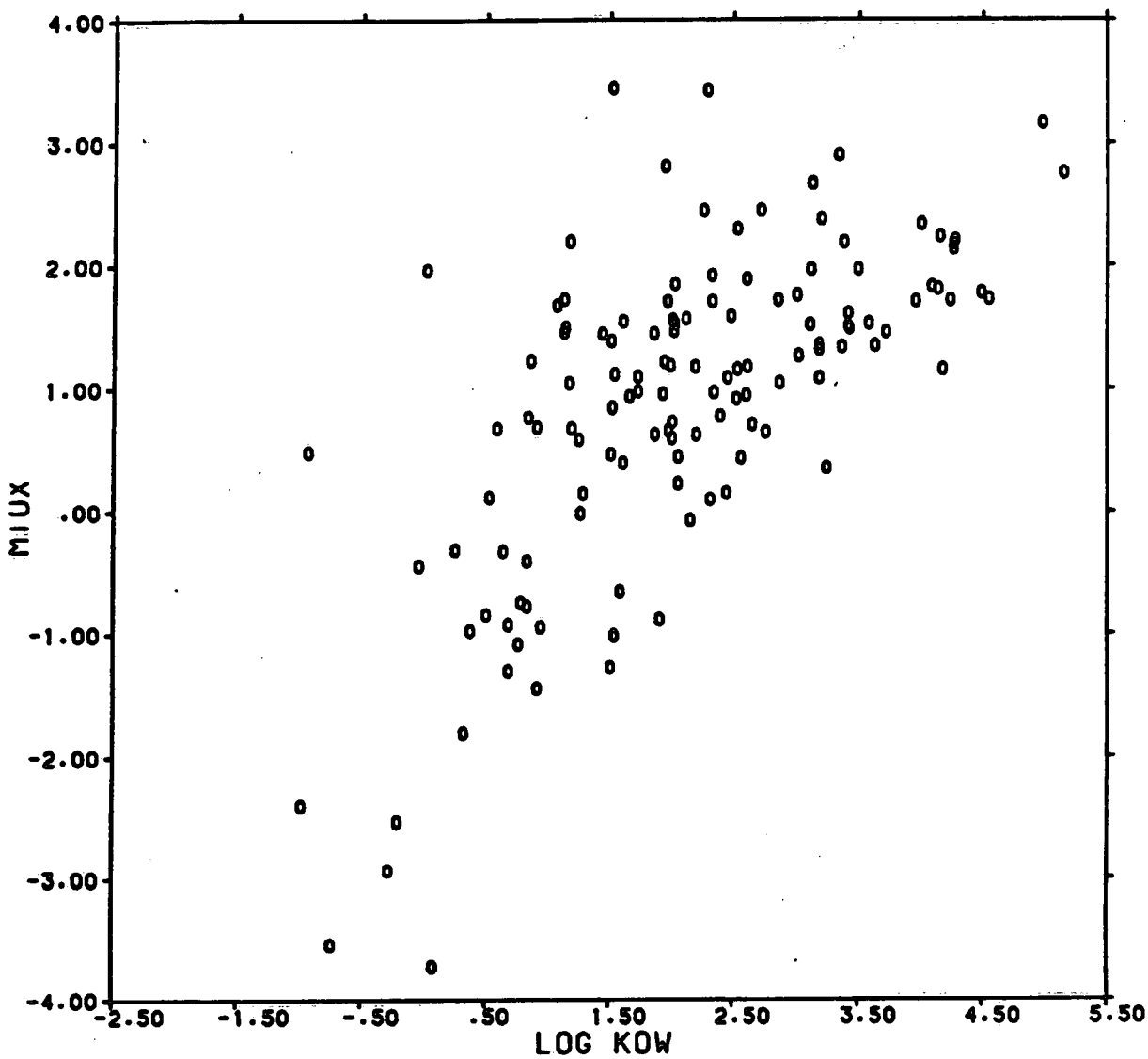

MTOX. FHM. LOG KOW. N=127
4.00
3.00
2.00
1.00
.00
-1.00
-2.00
-3.00
-4.00
MUX
-2.50
-1.50
-.50
.50
1.50
2.50
3.50
4.50
5.50
LOG KOW

FIGURE 6

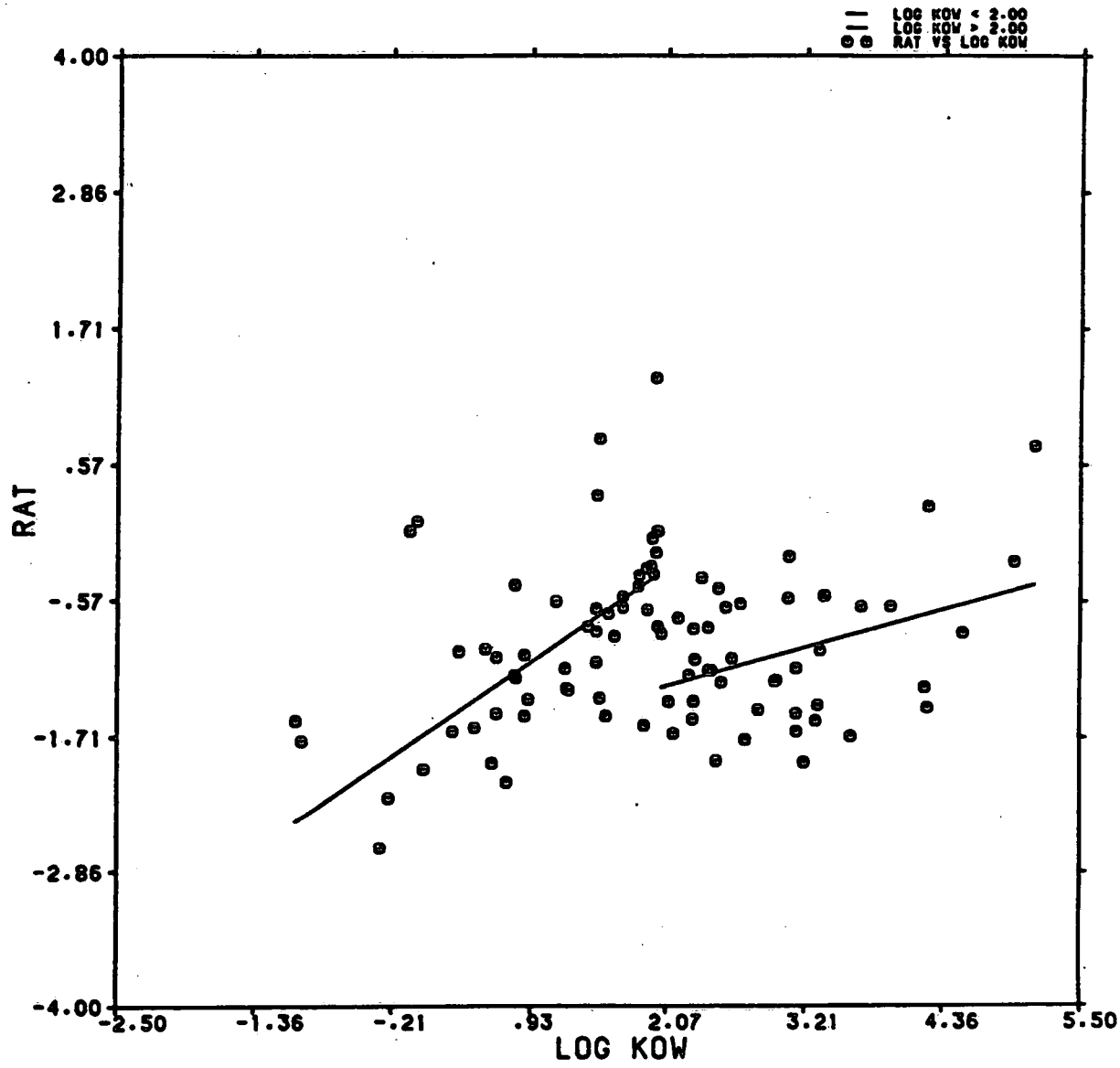
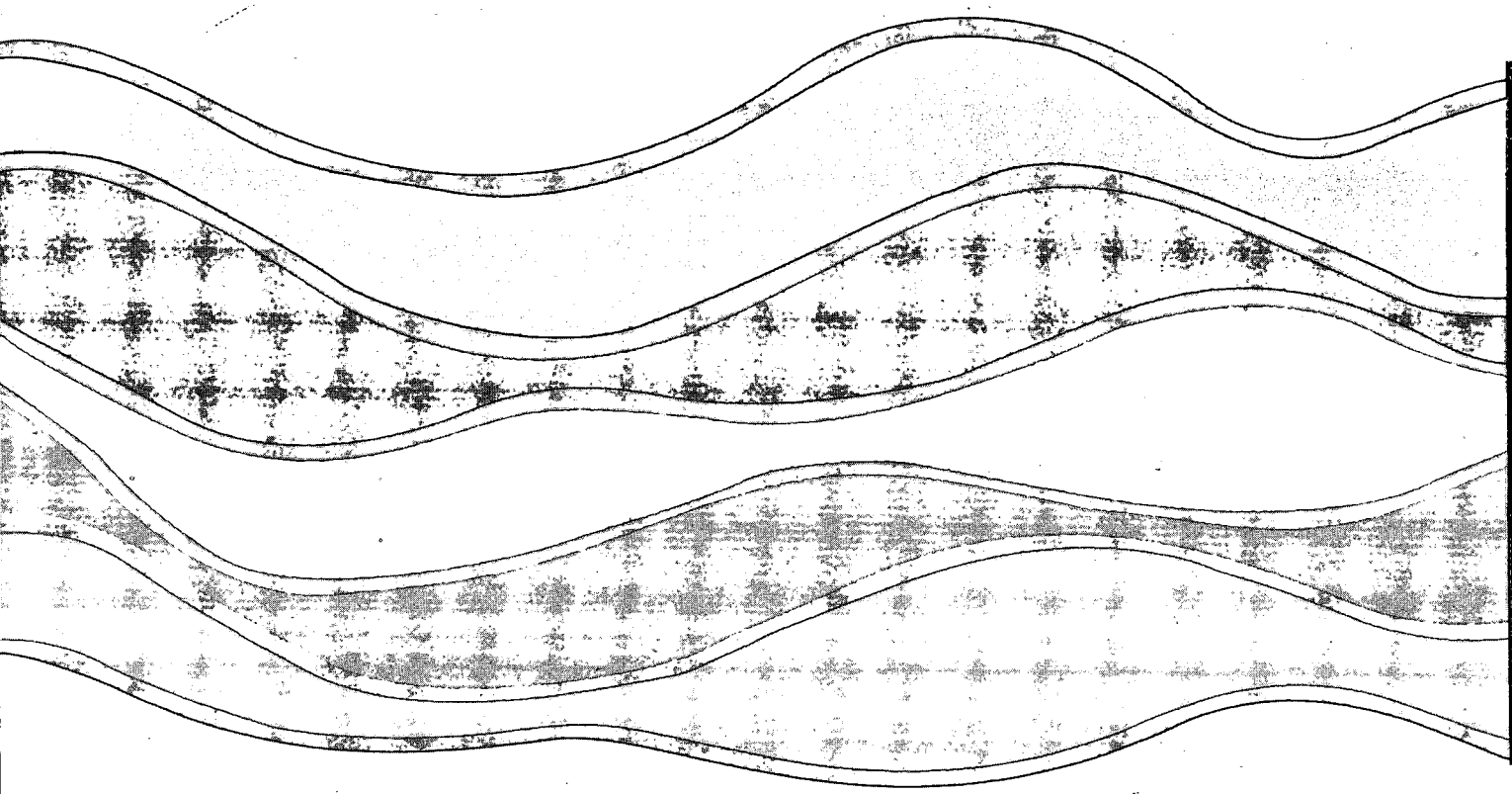

LOG KOW < 2.00
LOG KOW > 2.00
RAT VS LOG KOW
4.00
2.86
1.71
.57
-.57
-1.71
-2.86
-4.00
RAT
-2.50
-1.36
-.21
.93
2.07
3.21
4.36
5.50
LOG KOW

FIGURE 7



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