APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 5, 91–97 (1991)

Structure–activity relationships for organotin compounds on the red killifish *Oryzias latipes*

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The LC_{50} values of a series of 29 organotin compounds were determined for the red killifish (*Oryzias latipes*) according to an OECD test guideline. Their toxicities varied from 10^{-1} to 10^{-5} mmol dm^{-3} in five orders of magnitude. In this paper a quantitative structure–activity relationship (QSAR) study of these organotin compounds was carried out using physicochemical and topological parameters as independent variables. These parameters were found not to be good descriptors for estimating the LC_{50} values. However, when the term Index Value (IV), which is created as a new parameter and is defined by the number of phenyl or alkyl groups attached to the tin atom, was used, excellent regression equations to predict the toxicities of organotin compounds were obtained and a multiparametric relationship including IV, Information Index (I_D^w) and Mean Information Index ($\bar{I}_D^w$) showed the best correlation.

Keywords: Toxicity, organotin, quantitative structure–activity relationship (QSAR), Index Value (IV), Information Index (I_D^w), Mean Information Index ($\bar{I}_D^w$)

INTRODUCTION

The production of organotin compounds has increased owing to their wide applications for biocides, heat stabilizers, catalysts etc.[1-3] Tributyltins, used as antifouling paints for ships or fishing nets, have been paid special attention in recent years.[2,3]

Organotin compounds used in industry are generally less volatile[4] so these compounds would be likely to remain in the aquatic environment, and it is therefore very important to understand the ecotoxic effects of organotin compounds on aquatic organisms. From this viewpoint, environmental monitoring for organotin compounds has been continued in many countries, and much information on the toxicities of organotin compounds for various aquatic organisms has been reported.[5-10] However, these studies on toxicity were carried out mainly in relation to tributyltins. The (tri)organotin compounds released into the environment will be transformed into others, both physicochemically and biologically in the aquatic environment,[4,11,12] so quite large numbers of tin species will be found in the aquatic environment.

Therefore we should know the toxicities of all of these organotin compounds. Recently quantitative structure–activity relationships (QSAR) have been applied to analyze toxicities of the chemicals whose influences on the ecosystems cannot actually be measured.[13]

There are some reports which have applied QSAR to organotin compounds for aquatic organisms.[8,14-16] However, no reports on fish have been found, and the numbers of tested organotin compounds were rather small, 15 compounds at the most. It is important to measure the toxicity values of a series of organotin compounds in order to obtain better and more reliable results for QSAR values. In this paper, toxicities of 29 organotin compounds were measured according to the OECD test guideline No. 203[17] and used with QSAR values to elucidate the factors controlling their toxicities and also to predict their toxicities. We used some physicochemical and topological parameters as a molecular descriptor. As a physicochemical parameter, the n-octanol/water partition coefficient (log P) and molecular

This paper is based on work presented at the 1989 International Chemical Congress of Pacific Basin Societies held in December 1989 in Honolulu. The meeting was sponsored by the Chemical Society of Japan, The Chemical Institute of Canada and the American Chemical Society.

0268-2605/91/020091-07$05.00

Received 18 April 1990

weight (MW) were adopted. As the biophase is considered akin to octanol, log *P* is expected to correlate well with biological activities,[14,18] and many researchers have modeled toxicities towards various organisms successfully with log *P*. Molecular weight is clearly one property of a chemical which follows from its structure, and it is also related to permeability to the biophase.

As a topological parameter, molecular connectivity indices ($^1\chi$, $^1\chi^v$, $^3\chi_p$)[19,20] and a number of information-theoretic topological indices[21] (Wiener number (log(W)), information index [log(I_D^w)], mean information index ($\bar{I}_D^w$), information content (IC), structural information content (SIC), and complementary information content (CIC) were chosen.

These topological parameters can be directly derived from the manipulation of a two-dimensional formula, so these parameters are available to predict the effects of structurally heterogeneous chemicals in an ecotoxicological approach.

Further, we define Index Value (IV) as a new parameter, which was represented on the basis of the number of alkyl or phenyl groups attached to the tin atom; using this parameter (IV), the toxicities of organotin compounds were well predicted.

MATERIALS AND METHODS

Chemicals

The following tested organotin compounds were purchased commercially. Tetra-n-butyltin, tri-n-butyltin acetate, dimethyltin dichloride, di-n-butyltin dichloride and di-n-butyltin oxide were purchased from Merck. Triethyltin bromide, tri-n-butyltin methoxide, tri-n-butyltin ethoxide, di-n-butyltin dilaurate, diphenyltin dichloride, methyltin trichloride and phenyltin trichloride were purchased from Aldrich. Tetramethyltin, trimethyltin chloride, tri-n-butyltin chloride, triphenyltin chloride, and di-n-butyltin diacetate were bought from Kantoh Chemicals. Triphenyltin hydroxide, triphenyltin acetate, bis(tri-n-butyltin), bis(tri-n-butyltin)oxide and di-n-butyltin maleate were obtained from Wako Pure Chemicals. Tri-n-butyltin fluoride and mono-n-butyltin oxide were purchased from Tokyo Chemical Kogyo. Tetraphenyltin was obtained from Nakarai Chemicals. These chemicals were used without further purification.

n-Butyltrimethyltin, di-n-butyldimethyltin, n-butyltrimethyltin and tetrapropyltin were synthesized using Grignard reagents in our laboratory. These compounds were identified by mass spectrometry, and their purities confirmed by GC–FPD.

Acute toxicity test

The acute toxicity test on Red killifish *Oryzias latipes* was carried out according to the OECD test guideline No. 203.[17]

Oryzias lastipes samples were purchased live from the market, and acclimatized in the dechlorinated tap water for at least seven days. Mortality should be less than 5% of the population during acclimatization. Stock solutions of trimethyltin chloride and dimethyltin dichloride were prepared by being dissolved directly in water. The other chemicals were dissolved in a vehicle which consisted of dimethyl sulfoxide and HCO-40, a surfactant (Nikko Chemicals), at the ratio of 4:1, and aqueous stock solutions of concentration 1% or 10% were prepared. The test solutions were adjusted to the intended concentration through the following procedure: appropriate amounts of water were added to the stock solution, then dispersed with a biomixer (Nippon Seiki Co.), and in addition, this solution was further diluted with water to the intended concentration.

The test was semi-static, i.e., the test solutions were renewed every 24 h. Other test conditions were as follows: water, dechlorinated tap water; loading, 10 fish in 2 dm^3 test solution; concentration of test solution, at least five concentrations spaced by a constant factor not exceeding 1.8;[17] temperature, 20 ± 1 °C; duration, 96 h; light, one 16-hour photoperiod daily.

During the tests, numbers of deaths, pH and dissolved oxygen (DO) were measured every 24 hours. Control tests were practised both in the case of water and in solution containing the vehicle at the highest concentration. The mortality in the blank solution should be less than 10%.

Molecular properties

n-Octanol/water partition coefficient, log *P*

Eleven values of log *P* for the organotin compounds were obtained from the literature[8,17] and the other 12 values were calculated by the π method.[22]

Molecular Connectivity Indices (χ) and Valence Molecular Connectivity Indices (χ^v)[19, 20]

The Molecular Connectivity Indices (χ) and Valence Molecular Connectivity Indices (χ^v) were calculated from a hydrogen-suppressed graph. The basic calculation of these parameters followed the method in the literature,[19, 20] but in the calculation of χ^v, the formula for calculating δ^v was slightly modified, viz.

$$\delta^v = (Z^v - h)/(Z - Z^v - 1)$$

where Z^v, Z and h are the number of valence electrons, atomic number, and the number of hydrogen atoms, respectively.

In the QSAR studies, $^1\chi$ and $^1\chi^v$ have been often used because of the simplicity of calculation, and Yoshioka *et al.*[23] reported that $^3\chi_p$ was a good descriptor to estimate the toxicities of 123 chemicals on *Oryzias latipes*. We used $^1\chi$, $^1\chi^v$ and $^3\chi_p$ as parameters for the analysis of QSAR.

Wiener number (W), Information Index (I_D^w) and Mean Information Index ($\bar{I}_D^w$)[21, 24–26]

The Wiener number (W), Information Index (I_D^w), and Mean Information Index ($\bar{I}_D^w$) were calculated on the basis of the distance matrix ($N \times N$) according to a hydrogen-suppressed molecular graph. The calculation of these parameters was carried out by the literature method.[21, 24–26]

Information Content (IC), Structural Information Content (SIC) and Complementary Information Content (CIC).[21, 27, 28]

IC, SIC and CIC were calculated from the hydrogen-nonsuppressed molecular graph and the calculation formula were as defined in the literature.[21, 27, 28]

Multiple regression analysis was carried out with a stepwise method ($F = 2.0$).

RESULTS AND DISCUSSIONS

Acute toxicity test

The LC_{50} values obtained from acute toxicity tests on *Oryzias latipes* are shown in Table 1.

The toxicity values of a series of organotin compounds were found to occur over a wide range, 10^{-1}–10^{-5} mmol dm^{-3} at 48 h – LC_{50}, and the differences of toxicity depend upon the distinctions between their chemical structures.

Table 1 48h-LC_{50} values of organotin compounds in *Oryzias latipes*

No.	Chemical	48h-LC_{50} (mmol dm^{-3})
1	Tetramethyltin	3.60×10^{-2}
2	Tetra-n-propyltin	5.85×10^{-3}
3	Tetra-n-butyltin	1.50×10^{-2}
4	Tetraphenyltin	9.37×10^{-4}
5	n-Butyltrimethyltin	4.07×10^{-3}
6	Di-n-butyldimethyltin	3.08×10^{-3}
7	Tri-n-butylmethyltin	1.28×10^{-1}
8	Trimethyltin chloride	2.82×10^{-2}
9	Triethyltin bromide	2.62×10^{-3}
10	Tri-n-butyltin chloride	1.11×10^{-4}
11	Tri-n-butyltin fluoride	2.01×10^{-4}
12	Tri-n-butyltin methoxide	7.10×10^{-5}
13	Tri-n-butyltin ethoxide	7.40×10^{-5}
14	Tri-n-butyltin acetate	2.26×10^{-4}
15	Triphenyltin chloride	1.66×10^{-4}
16	Triphenyltin hydroxide	1.80×10^{-4}
17	Triphenyltin acetate	1.81×10^{-4}
18	Bis(tri-n-butyltin)	4.98×10^{-4}
19	Bis(tri-n-butyltin)oxide	1.21×10^{-4}
20	Dimethyltin dichloride	2.73×10^{-2}
21	Di-n-butyltin dichloride	1.91×10^{-2}
22	Di-n-butyltin diacetate	1.07×10^{-2}
23	Di-n-butyltin dilaurate	3.23×10^{-3}
24	Di-n-butyltin maleate	3.78×10^{-2}
25	Di-n-butyltin oxide	3.37×10^{-3}
26	Diphenyltin dichloride	8.90×10^{-2}
27	n-Butyltin trichloride	1.35×10^{-1}
28	Mono-n-butyltin oxide	2.63×10^{-1}
29	Phenyltin trichloride	3.61×10^{-1}

Especially, tributyltins and triphenyltins showed higher toxicities than any other organotin compound, and their levels of toxicity were 10^{-4}–10^{-5} mmol dm^{-3}. These LC_{50} values, which correspond to 10^{-1}–10^{-2} mg dm^{-3}, at a fairly low concentration level, and this suggests that various aquatic organisms might easily suffer damage from them, so it is important to continue environmental monitoring for these compounds.

Application of QSAR

All the eigenvalues applied to QSAR are shown in Table 2. The toxicity values are exhibited by log(1/48 h LC_{50}). Linear correlations were analyzed in the relationship between each eigenvalue of each organotin compounds as an independent variable and log(1/LC_{50}) as a dependent variable. The results of the regression analyses are shown in Table 3. In these analyses, good linear correlations could not be obtained. $\bar{I}_D^w$ indicated the best

Table 2 Physicochemical and topological parameters of organotin compounds

No.	Chemical	log(1/LC_{50})	MW	log$P$	$^1\chi_p$	$^1\chi_p^v$	$^3\chi_p$	CIC	SIC	IC	log(W)	log(I_D^w)	$\bar{I}_D^w$
1	Tetramethyltin	1.444	178.7	−2.19[a]	2.60	13.41	0.00	3.00	0.266	1.09	1.20	1.72	3.25
2	Tetra-n-propyltin	2.233	290.7	2.04[a]	6.24	14.31	3.12	4.06	0.242	1.29	2.41	3.20	6.12
3	Tetra-n-butyltin	1.824	347.2	3.90[a]	8.24	16.31	4.24	4.47	0.219	1.25	2.75	3.59	6.91
4	Tetraphenyltin	2.028	427.1	4.39[a]	14.31	14.42	9.79	4.02	0.268	1.47	3.32	4.25	8.49
5	n-Butyltrimethyltin	2.390	221.0	−0.54[b]	3.56	14.13	1.28	3.38	0.282	1.32	1.85	2.52	4.62
6	Di-n-butyldimethyltin	2.511	262.7	1.19[b]	5.12	14.86	2.41	3.82	0.256	1.31	2.26	3.00	5.57
7	Tri-n-butylmethyltin	0.893	305.0	2.36[b]	6.68	15.58	3.40	4.18	0.235	1.28	2.54	3.34	6.31
8	Trimethyltin chloride	1.550	199.2	−2.30[a]	2.00	13.86	0.00	2.71	0.288	1.09	1.20	1.72	3.25
9	Trimethyltin bromide	2.582	285.8	−1.80[b]	3.68	16.35	2.56	3.20	0.294	1.33	1.81	2.48	4.68
10	Tri-n-butyltin chloride	3.955	325.4	2.60[a]	6.68	16.03	3.40	4.09	0.236	1.26	2.54	3.34	6.31
11	Tri-n-butyltin fluoride	3.697	309.0	—	6.68	13.50	5.12	2.71	0.476	2.46	2.54	3.34	6.31
12	Tri-n-butyltin methoxide	4.149	321.1	1.78[b]	7.28	14.01	3.93	4.01	0.270	1.48	2.60	3.42	6.53
13	Tri-n-butyltin ethoxide	4.131	335.1	2.18[b]	7.74	14.60	3.96	4.09	0.267	1.49	2.67	3.50	6.73
14	Tri-n-butyltin acetate	3.646	349.1	1.16[b]	8.10	14.51	4.02	3.91	0.296	1.65	2.74	3.58	6.91
15	Triphenyltin chloride	3.780	384.5	2.65[a]	11.23	14.61	7.52	3.64	0.291	1.49	3.08	3.97	7.78
16	Triphenyltin hydroxide	3.745	367.0	1.27[b]	9.82	12.13	7.46	3.39	0.345	1.78	2.86	3.73	7.40
17	Triphenyltin acetate	3.742	409.0	1.30[b]	11.23	13.04	7.86	3.18	0.407	2.18	3.01	3.90	7.83
18	Bis(tri-n-butyltin)	3.303	580.1	—	12.61	35.70	7.19	5.04	0.203	1.28	3.19	4.10	8.19
19	Bis(tri-n-butyltin)oxide	3.917	596.0	2.29[a]	13.07	27.20	7.11	4.98	0.215	1.36	3.26	4.17	8.29
20	Dimethyltin dichloride	1.564	219.7	−3.10[a]	2.00	11.77	0.00	2.36	0.317	1.10	1.20	1.72	3.25
21	Di-n-butyltin dichloride	1.719	303.8	1.49[a]	5.12	15.76	2.41	3.23	0.233	1.13	2.26	3.00	5.57
22	Di-n-butyltin diacetate	1.971	351.0	−1.21[b]	7.95	12.71	3.80	3.40	0.365	1.95	2.73	3.57	6.92
23	Di-n-butyltin dilaurate	2.491	631.6	—	18.03	22.83	9.29	5.04	0.241	1.60	3.77	4.73	9.10
24	Di-n-butyltin maleate	1.423	291.0	—	8.12	12.62	6.90	1.69	0.644	3.06	2.71	3.55	6.91
25	Di-n-butyltin oxide	2.472	248.9	—	4.81	4.33	2.10	3.31	0.312	1.50	2.17	2.89	5.26
26	Diphenyltin dichloride	1.051	344.0	1.40[b]	7.21	14.76	5.32	3.13	0.326	1.51	2.55	3.36	6.52
27	n-Butyltin trichloride	0.870	282.2	0.35[a]	3.56	15.48	1.28	2.93	0.284	1.16	1.85	2.52	4.62
28	Mono-n-butyltin oxide	0.580	209.0	—	3.27	6.95	1.14	1.96	0.521	2.13	1.72	2.34	4.20
29	Phenyltin trichloride	0.442	302.0	1.15[b]	4.61	14.97	2.83	2.37	0.392	1.53	2.16	2.78	5.33

—, Not determined

[a]Data from Ref. 16. [b]Calculated by the π method.

MW = molecular weight, log P = noctanol/water partition coefficient

$^1\chi_p$, $^1\chi_p^v$ and $^3\chi_p$ = molecular connectivity indices[19, 20]

CIC = complementary information content[21] SIC = structural information content[21]

IC = information content[21] W = Wiener number[21] I_D^w = information index[21]

$\bar{I}_D^w$ = mean information index[21]

Table 3 Linear correlation of log ($1/LC_{50}$) with each parameter

Independent variables (X)	Equation $\log(1/LC_{50}) = a(X) + b$		Statistics	
	a	b	n	r^a
MW	0.005	0.898	29	0.432
log$P$	0.209	2.275	23	0.328
$^1\chi_p$	0.135	1.437	29	0.452
$^1\chi_p^v$	0.005	1.576	29	0.263
$^3\chi_p$	0.185	1.654	29	0.440
log(W)	0.901	0.214	29	0.495
log(I_D^w)	0.769	−0.058	29	0.504
I_D^w	0.375	0.098	29	0.510
IC	0.219	2.081	29	0.084
SIC	−2.732	3.264	29	−0.230
CIC	0.691	0.005	29	0.507

[a] r = coefficient of correlation.0

correlation among them, but its coefficient of correlation was still only 0.510. Therefore multiple regression analyses were carried out with a stepwise method ($F = 2.0$), and the regression equation obtained with two variables is shown as Eqn [1]:

$$\log(1/LC_{50}) = 4.388(IC) - 20.879(SIC) + 2.392 \quad (r = 0.702) \qquad [1]$$

However, from the above results, the regression equations giving the general toxicities could not be estimated adequately.

On the other hand, in order to investigate the character of organotin compounds, we compared 23 organotin compounds (no log P values were available for the other six) with 123 other chemicals which are structurally non-specific and have already been studied as to the relationship between log P and the toxicities for *Oryzias latipes*, by Yoshioka *et al.*[23] The results are shown in Fig. 1.

The 123 other chemicals represented comparatively good correlations for log P ($r = 0.738$). However, the correlations became much poorer when organotin compounds were included. Moreover, organotin compounds with higher values of log P indicated various toxicities, and those with lower values of log P showed higher

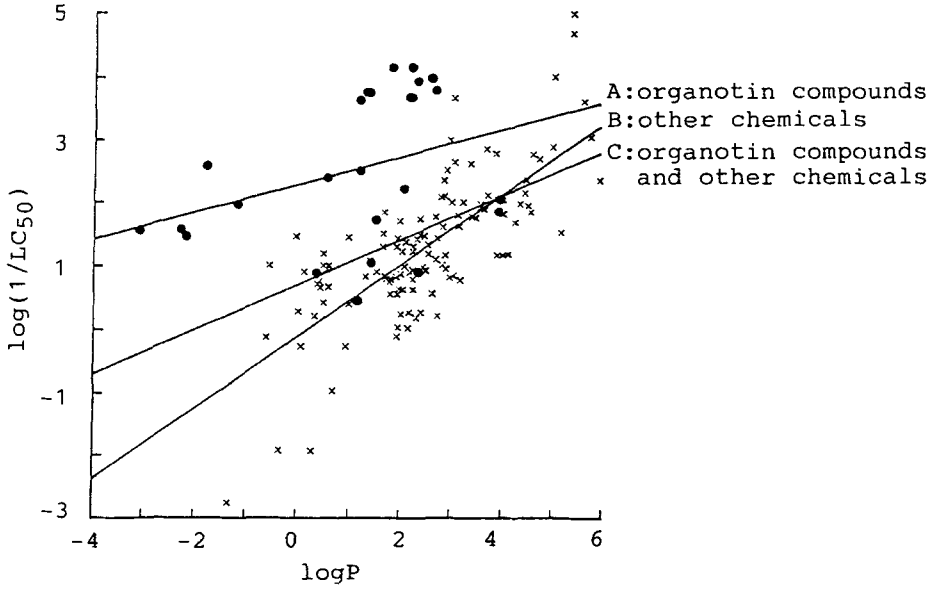

Figure 1 Relationship between n-octanol/water partition coefficient (log P) and toxicity in *Oryzias latipes* [$\log(1/LC_{50})$]. ●, organotin compounds ($n = 23$); ×, other chemicals ($n = 123$). Regression equations:
A: $\log(1/LC_{50}) = 0.208 \log P + 2.275$ ($n = 23$, $r = 0.328$)
B: $\log(1/LC_{50}) = 0.563 \log P - 0.093$ ($n = 123$, $r = 0.738$)
C: $\log(1/LC_{50}) = 0.343 \log P + 1.070$ ($n = 147$, $r = 0.456$)

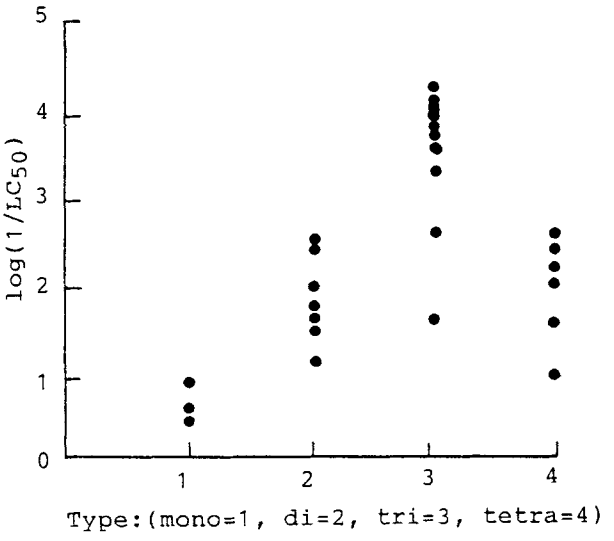

Figure 2 Relationship between the type of organotin compound and $\log(1/LC_{50})$.

toxicity in comparison with the 123 other chemicals.

Log *P* is the most popular description in relation to the membrane permeability based on the Linear Free-Energy Relationship (LFER) cf Hansch *et al.*[29] is the most popular term as a descriptor in relation to membrane permeability, but log *P* was not suitable regarding the toxicities of the 29 organotin compounds. Vighi and Calamari[16] also reported that reliable correlations between log *P* values of 15 organotin compounds and $\log(1/EC_{50})$ values on the water flea (*Daphnia magna*) could not be acquired. Laughlin *et al.*[15] showed that the $\log(1/LC_{50})$ values of 15 organotin compounds (seven diorganotin compounds and eight triorganotin compounds) on the marine crab larvae (*Rhithropaenaeus harrisii*) could be predictably explained using the total surface area (TSA) of their molecules, which related to the factors controlled by their hydrophobic behavior.

However, we could not obtain good correlations with their molecular weight as a parameter, which might be correlatable for TSA, so the toxicities of the 29 organotin compounds cannot be estimated only by their hydrophobicity.

The series of 29 organotin compounds was then classified on the basis of the number of alkyl or phenyl groups attached to the tin atom, and the relationship between the type of organotin compounds and $\log(1/LC_{50})$ is shown in Fig. 2. The toxicities of these organotin compounds depended on the number of alkyl or phenyl groups: $\log(1/LC_{50})$ values of mono-organotin compounds were between 0.44 and 0.87, diorganotins were beween 1.05 and 2.49, triorganotins were between 1.55 and 4.15, and tetraorganotins were 0.89 and 2.51. In this way the toxicities of organotin compounds were as follows: tri > di = tetra > mono. We therefore defined the Index Value (IV) as a new parameter, the values of which are mono = 1, di = 2, tri = 3, tetra = 2. When the regression analysis was carried out with this parameter (IV), fairly good regression formulae to predict their toxicities were obtained:

$$\log(1/LC_{50}) = 1.219(IV) - 1.093 \quad (n = 29,\ r = 0.857) \quad [3]$$

$$\log(1/LC_{50}) = 1.374(IV) + 0.382\log(I_D^w) - 1.986 \quad (n = 29,\ r = 0.889) \quad [4]$$

$$\log(1/LC50) = 1.504(IV) + 3.819\log(I_D^w) - 1.681(\bar{I}_D^w) - 2.916 \quad (n = 29,\ r = 0.907) \quad [5]$$

The relations between the toxicities observed in the acute toxicity test and the toxicities estimated by regression formulae with three independent variables showed fairly reliable correlation, as shown in Fig. 3.

CONCLUSIONS

The series of 29 organotin compounds tested showed various toxicities according to the differences in their structures. The toxicities of these organotin compounds did not depend upon their hydrophobic characters, which were expected to correlate well with log LC_{50} and bioconcentration factors for aquatic organisms in relation to transmission through their membranes. Laughlin *et al.*[15] reported that the toxicities of some organotin compounds in crab larvae showed poor correlations with other parameters which were related to steric configuration or electronic effects.[14,15] So

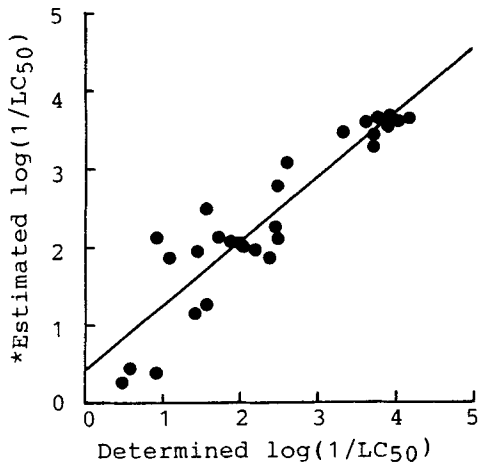

Figure 3 Relationship between estimated and determined $\log(1/LC_{50})$ values. The estimated values were obtained by the following equation:

$$\log(1/LC_{50}) = 1.504(IV) + 3.819\log(I_D^w) - 1.681(\bar{I}_D^w) - 2.961$$

$$(n = 29,\ r = 0.907)$$

possible factors which might produce the various toxicities shown cannot be clarified psysicochemically on the basis of differences in molecular structure.

However, on predicting the ecotoxicological effects of organotin compounds on fish, good regression equations were obtained from 29 organotin compounds with the Index Value (IV) as a parameter which is defined by the number of phenyl or alkyl group attached to the tin atom. In addition to the IV, triparametric regression equations using the Information Index (I_D^w) and Mean Information Index ($\bar{I}_D^w$), which are topological parameters in relation to molecular size, explained their toxicities in fish comprehensively.

Acknowledgements We thank Mr Manabu Nakatani, Miss Izumi Fujiwara and Mr Hiroyuki Yano for their contributions. This work was supported by the Grants in Aid for Scientific Research from the Ministry of Education, Culture and Science, Japan.

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