Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(12):349-358

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

The quantitative ion character-activity relationship between metal ionic properties and their toxicity order numbers through cluster analysis

X. P. Li, L. Jiang, S. S. Li and Y. Li*

Resource and Environmental Research Academy, North China Electric Power University, Beijing, China

---

ABSTRACT

The Quantitative Ion Character-Activity Relationship (QICAR) model between metal ionic properties and toxicity order numbers (TON) was established assisted with cluster analysis to find out typical metal ionic properties. Means while, the multicollinearity among the typical metal ionic properties was minimized by principal component analysis during the modeling and obtaining .the QICAR model by multiple linear regression analysis as follows: $TON = -70.675AR/AW - 0.353|lgK_{OH}| - 28.312\sigma_p - 0.537\Delta E_0 + 2.436X_m^2r + 0.240AN - 0.024Z^{*2}/r + 0.475N + 26.033$. It has satisfactory predicted ability with Nash-Suttcliffe Simulation Efficiency Coefficient (NSC) of 0.91 and 0.85formodel building and testing respectively. The metal ionic propertiesX_m^2r, AN and N have positive effects on the model, while the metal ionic properties AR/AW, $|lgK_{OH}|$, σ_p, ΔE_0 and Z^{*2}/r negatively influence the model. Finally, sensitivity analysis of the metal ionic properties in QICAR model was carried out to show which metal ionic properties have more impact on TON, indicating different impact degree of the metal ionic properties on each metal ion.

Keywords: quantitative ion character-activity relationship, toxicity order numbers, cluster analysis, principal component analysis, sensitivity analysis

---

INTRODUCTION

Heavy metals, from various industrial processes, agricultural activities, domestic wastes and vehicle exhaust emissions, are often considered one of the most serious pollutants for their high toxicity, bioaccumulation and persistence in the environment [1-4].They can alter the biochemical cycles [5].The studies on heavy metals' pollution and their toxicity prediction have received increasing attention in recent years [6]. There are many factors affecting the toxicity of heavy metals and the three major factors are metal ionic properties(for example, atomic radius, oxidation state, electronegativity, etc.), organism receptor (for example, species, sex, age, etc.) and environmental conditions (for example, temperature, pH, exposure length, etc.) [7]. Up till now, most studies have been done only focusing on environmental conditions [8], while the other two factors tend to be ignored.

The Quantitative Structure-Activity Relationship (QSAR) model has been used extensively to express structural molecular properties with functions (for example, physicochemical properties, biological activities, toxicity, etc.) for classes of organic compounds by means of statistical methods. In the 1990s, Newman et al. developed the Quantitative Ion Character-Activity Relationship (QICAR)model to predict the relative toxicity of metal ions [9].The approach has been successfully applied in various effects, species and media to predict the relative toxicity of metal ions since then [9-11]. Simple linear regression models using one metal ionic property $|\log K_{OH}|$,σ_p, orX_m^2r were built by Mccloskey, Wolterbeek and Tatara, respectively [11-13]. A model that includes two metal ionic properties $lgAN/\Delta IP$ and ΔE_0approved its applicability through tests using toxicity data of *Daphniamagna* by Kaiser et al [14].All of those QICAR models above incorporated very few metal ionic properties and ignored the impact of other metal ionic properties.

Cluster analysis, known as automatic classification, numerical taxonomy, bryology and typological analysis [15-16], is designed to detect hidden groups or clusters, in which the elements behave similarly to each other [17-18]. The similarity is generally defined using the measurement of distance and calculated using the difference between the measurements [19].The classification of variables could enhance our understanding of the internal rules for variables in the same group and find typical variables in each group [20].

The goals of the current study are to select typical metal ionic properties to build a QICAR model and to predict the toxicity of metal ions. Cluster analysis is applied to divide the metal ionic properties into several groups. In each group we choose the typical metal ionic property through correlation analysis and the QICAR model will be built by multiple linear regression analysis after minimizing the multicollinearity among the typical metal ionic properties using principal component analysis. Then, sensitivity analysis is adopted to judge the impact degree of the typical metal ionic properties of the model.

EXPERIMENTAL SECTION

Toxicity Data

Metal ion toxicity data varied largely in exposure time, organism receptors and ambient conditions. Therefore, Wolterbeek and Verburg evaluated 80metal ions' toxicity using 30 data sets from different literatures[13]. For each data set, the calculated toxicities were ordered numerically by relative numbering. After doing so for the 30 data sets, each selected metal ion could be given an averaged number. Toxicity order numbers (TON) increased with toxicities.

In the current study, the TONs of twenty metal ions (Ag^+, Ba^{2+}, Ca^{2+},Cd^{2+},Co^{2+}, Cr^{3+}, Cs^+, Cu^{2+}, Fe^{3+}, Hg^{2+}, K^+, La^{3+}, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Sr^{2+}, Zn^{2+}) were used for building the model and other seven (Al^{3+}, Bi^{3+}, Fe^{2+}, Rb^+, Sb^{3+}, Sc^{3+}, Y^{3+}) were used for model testing (shown in Table 1 and 2).The 15min -lgEC_{50} for *photobacterium phosphoreum* of nine metal ions(Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, K^+, Mn^{2+}, Ni^{2+}, Sr^{2+}, Zn^{2+}) obtained were used for validating model.

Data of Metal Ionic Properties

We denoted metal ionic properties *OX* as the oxidation state; ΔE_0 as the absolute difference in electrochemical potential between the ion and its first stable reduced state; *IP* as the ionization potential; X_m as the electronegativity; *AR* as the atomic radius; *r* as the Pauling ionic radius; *AW* as the atomic weight; *AN* as the atomic number; ΔIP as the difference in ionization potential between *OX* and OX^{-1}; $|\log K_{OH}|$ as the absolute value of the log of the first hydrolysis constant; σ_p as the softness index; *Z** as the effective ionic charge; *N* as the ionic electron number for valence shell. In addition, there are several other metal ionic properties, which are some combination of the above. They are *AR/AW*, $X_m^2 r$, *AN*/ΔIP, Z^2/r (*Z*=ionic charge), Z/r^2, Z/AR^2, *Z*/*r*, *Z*/*AR* and Z^{*2}/r [12-13, 21-23].

Experimental Methods

The stock solutions of the nine tested metal ions were freshly prepared by dissolving the following nitrates in deionized water: $Cu(NO_3)_2 \cdot 3H_2O$ provided by Tianjin No. 3 Chemical Reagent Factory; $Cd(NO_3)_2 \cdot 4H_2O$ provided by Shanghai Jinshan Tingxin Chemical Reagent Factory; $Ni(NO_3)_2 \cdot 6H_2O$ provided by Beijing Yili Fine Chemical Co., Ltd.; $Co(NO_3)_2 \cdot 6H_2O$ provided by Tianjin Bodi Chemical Co., Ltd.; KNO_3 provided by Beijing Chemical Factory; $Zn(NO_3)_2 \cdot 6H_2O$, $Cr(NO_3)_3 \cdot 9H_2O$, $Mn(NO_3)_2$ and $Sr(NO_3)_2$ provided by Tianjin Guangfu Fine Chemical Research Institute.

The toxicities of the nine metal ions were evaluated using the *photobacterium phosphoreum* in freeze-dried form (provided by Institute of Soil Science, Chinese Academy of Sciences), which was activated prior to testing by the reconstitution solution. Since the *photobacterium phosphoreum* is one of the marine organisms, the adjustment for the osmotic pressure of the samples was applied to obtain a 2% salinity using NaCl. The light emission of the *photobacterium phosphoreum* through direct contact with the samples was measured using Biological Toxicity TesterDXY-2 (provided by Institute of Soil Science, Chinese Academy of Sciences)within an exposure time of 15minutes. The toxicities of the nine metal ions were measured using the National Standard Method of the People's Republic of China GB/T 15441-1995 (Water quality-Determination of the acute toxicity-Luminescent bacteria test).

Data Analysis

Cluster analysis, correlation analysis, principal component analysis, multiple linear regression analysis and sensitivity analysis were applied in the current study. Cluster analysis was used to place the metal ionic properties with similar behavior into groups. Correlation analysis was used to select the metal ionic properties which have the highest correlation with TON, and will help reduce the data needed.

Table 1Metal ionic property and TONs of twenty metal ions

Metal ions	*OX*	ΔE_0	*IP*	X_m	*AR*	*r*	*AW*	*AN*	*AR*/*AW*	ΔIP	$\lvert \lg K_{OH} \rvert$	$X_m^2 r$	Z^2/r	*AN*/ΔIP	σ_p	Z/r^2	Z/AR^2	*Z*/*r*	*Z*/*AR*	*Z**	Z^{*2}/r	*N*	TON
Ag^+	1	0.80	7.58	1.93	1.52	1.15	107.87	47	0.0141	7.58	11.0	4.28	0.87	6.20	0.074	0.76	0.4328	0.87	0.6579	3.70	11.90	18	49.4
Ba^{2+}	2	2.91	10.01	0.89	2.17	1.42	137.34	56	0.0158	4.80	13.4	1.12	2.82	11.67	0.183	0.99	0.4247	1.41	0.9217	3.20	7.21	8	32.6
Ca^{2+}	2	2.87	11.88	1.00	1.91	1.00	40.08	20	0.0477	5.76	12.5	1.00	4.00	3.47	0.181	2.00	0.5482	2.00	1.0471	3.20	10.24	8	16.1
Cd^{2+}	2	0.40	16.92	1.69	1.48	0.95	112.40	48	0.0132	7.92	9.7	2.71	4.21	6.06	0.081	2.22	0.9131	2.11	1.3514	4.70	23.25	18	52.0
Co^{2+}	2	0.28	17.09	1.91	1.25	0.65	58.93	27	0.0212	9.21	9.8	2.37	6.15	2.93	0.130	4.73	1.2800	3.08	1.6000	4.25	27.79	15	39.0
Cr^{3+}	3	0.41	30.97	1.66	1.25	0.62	52.00	24	0.0240	14.48	3.7	1.71	14.52	1.66	0.107	7.80	1.9200	4.84	2.4000	4.65	34.88	11	32.3
Cs^+	1	3.03	3.90	0.79	2.62	1.74	132.91	55	0.0197	3.90	0.0	1.09	0.57	14.10	0.218	0.33	0.1457	0.57	0.3817	2.20	2.78	8	34.6
Cu^{2+}	2	0.15	20.30	1.65	1.35	0.73	63.54	29	0.0212	12.57	8.0	1.99	5.48	2.31	0.104	3.75	1.0974	2.74	1.4815	4.55	28.36	17	40.0
Fe^{3+}	3	0.77	30.66	1.83	1.24	0.55	55.85	26	0.0222	14.46	2.2	1.84	16.36	1.80	0.097	9.92	1.9511	5.45	2.4194	4.95	44.55	13	29.8
Hg^{2+}	2	0.92	18.77	2.00	1.48	1.02	200.59	80	0.0074	8.33	3.7	4.08	3.92	9.60	0.065	1.92	0.9131	1.96	1.3514	4.70	21.66	18	62.1
K^+	1	2.93	4.34	0.82	2.31	1.51	39.10	19	0.0591	4.34	16.0	1.02	0.66	4.38	0.232	0.44	0.1874	0.66	0.4329	2.20	3.21	8	19.7
La^{3+}	3	2.38	19.19	1.10	1.87	1.16	138.91	57	0.0135	8.13	9.0	1.40	7.76	7.01	0.171	2.23	0.8579	2.59	1.6043	4.20	15.21	8	33.3
Li^+	1	3.05	5.39	0.98	1.52	0.76	6.94	3	0.2190	5.39	14.2	0.73	1.32	0.56	0.247	1.73	0.4328	1.32	0.6579	1.30	2.22	2	11.5
Mg^{2+}	2	2.37	15.04	1.31	1.55	0.72	24.31	12	0.0638	7.39	11.4	1.24	5.56	1.62	0.167	3.86	0.8325	2.78	1.2903	3.20	14.22	8	14.7
Mn^{2+}	2	1.19	15.65	1.55	1.12	0.67	54.94	25	0.0204	8.21	10.6	1.61	5.97	3.05	0.125	4.46	1.5944	2.99	1.7857	3.95	23.29	13	32.8
Na^+	1	2.71	5.14	0.93	1.86	1.02	22.99	11	0.0809	5.14	14.8	0.88	0.98	2.14	0.211	0.96	0.2891	0.98	0.5376	2.20	4.75	8	15.9
Ni^{2+}	2	0.26	18.18	1.90	1.25	0.69	58.71	28	0.0213	10.54	8.9	2.49	5.80	2.66	0.126	4.20	1.2800	2.90	1.6000	4.40	28.06	16	39.0
Pb^{2+}	2	0.13	15.04	2.33	1.54	1.19	207.19	82	0.0074	7.62	8.8	6.46	3.36	10.76	0.131	1.41	0.8433	1.68	1.2987	6.00	30.25	20	65.3
Sr^{2+}	2	2.90	11.04	0.95	2.07	1.26	87.62	38	0.0236	5.34	13.0	1.14	3.17	7.12	0.174	1.26	0.4668	1.59	0.9662	3.20	8.13	8	25.3
Zn^{2+}	2	0.76	17.97	1.81	1.31	0.74	65.37	30	0.0200	8.57	9.0	2.42	5.41	3.50	0.115	3.65	1.1654	2.70	1.5267	4.70	29.85	18	35.6

Table 2 Metal ionic properties and TONs of seven metal ions

Metal ions	*AR*/*AW*	$\lvert \lg K_{OH} \rvert$	σ_p	ΔE_0	$X_m^2 r$	*AN*	Z^{*2}/r	*N*	TON
Al^{3+}	0.0515	5.0	0.136	1.66	1.40	13	32.67	8	15.1
Bi^{3+}	0.0070	1.6	0.113	0.20	4.20	83	47.57	20	64.8
Fe^{2+}	0.0222	8.3	0.129	0.45	2.04	26	27.56	14	36.4
Rb^+	0.0284	0.0	0.229	2.98	1.08	37	3.01	8	28.8
Sb^{3+}	0.0116	0.0	0.119	0.66	3.19	51	64.47	20	50.9
Sc^{3+}	0.0360	5.1	0.140	2.08	1.39	21	23.52	8	18.3
Y^{3+}	0.0200	8.3	0.147	2.37	1.52	39	17.29	8	25.5

Principal component analysis is an important multivariate statistical analysis method. Its goals are to extract the most important information from the data set, to compress the size of the data set by keeping only this important information, and to simplify the description of the data set. For achieving these goals, principal component analysis generates new variables called principal components(PCs) which are obtained by weighted linear combinations of the original variables [24].Then we apply multiple linear regression analysis, taking the PCs which account for the majority proportion of variance as independent variables and TON as the dependent variable, to estimate the impact of the metal ionic properties on TON.

The application of sensitivity analysis is to judge the critical metal ionic property's impact on TON. Sensitivity analysis is defined as "the study of how the uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input" [25].It is an indispensable part of optimization design.

RESULTS AND DISCUSSION

Cluster Analysis of Metal Ionic Properties

We did a cluster analysis on all of the metal ionic properties in Table 3.They were artificially divided into 11 groups based on the dendrogram in Fig. 1. Table 3 also shows the results of the correlation analysis between the twenty two metal ionic properties and TON. Only one metal ionic property in each group was selected by the correlation maximum method, which is *AR*/*AW*, $|\lg K_{OH}|$, σ_p, *AR*, ΔE_0, $X_m^2 r$, *AN*, Z/r^2, Z^{*2}/r, *N* and *OX*.

AR (*sig*.=0.221), Z/r^2 (*sig*.=0.872) and *OX* (*sig*.=0.453), in the selected metal ionic properties mentioned above, did not reach the significant level (*sig*.<0.05), which means that they did not have significant correlation with TON. So, we discarded them in our following analysis. Finally, eight metal ionic properties, including *AR*/*AW*, $|\lg K_{OH}|$, σ_p,ΔE_0, $X_m^2 r$, *AN*, Z^{*2}/r and *N*, were selected.

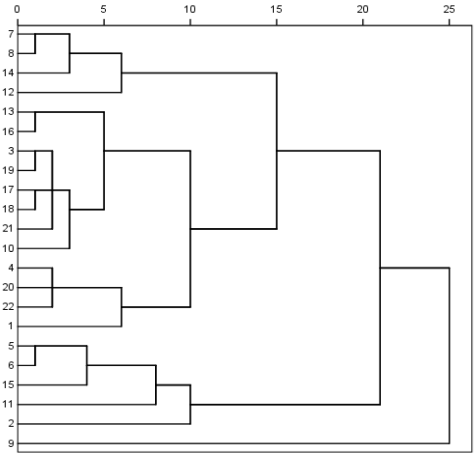

Fig. 1Dendrogram constructed by cluster analysis of the twenty two metal ionic properties

Principal Component Analysis of Metal Ionic Properties

Multicollinearity refers to the approximate linear relation among the variables, which means a variable can be linearly expressed by others. Strong multicollinearity among variables often decreases the accuracy of parameter estimation, enlarges model error and damages model stability [26]. Therefore, minimizing multicollinearity is essential before building a multiple linear regression model. In order to minimize the multicollinearity of the selected eight metal ionic properties, we did a principal component analysis. It shows in Table 4 that there is significant multicollinearity (*sig*. < 0.05) among the eight metal ionic properties through the correlation analysis.

Table 3Results of cluster analysis of the twenty two metal ionic properties and correlation analysis between the twenty two metal ionic properties and TON

Metal ionic properties	N	Cluster analysis	Correlation analysis	
		Group	*R*	*sig.* (2-tailed)
AR/*AW*	20	1	-0.631**	0.003
$\|\lg K_{OH}\|$	20	2	-0.456*	0.043
σ_p	20	3	-0.729**	< 0.001
R	20	4	0.066	0.783
AR	20	4	-0.287	0.221
ΔE_0	20	5	-0.708**	< 0.001
$X_m^2 r$	20	6	0.870**	< 0.001
AN/Δ*IP*	20	7	0.512*	0.021
AN	20	7	0.833**	< 0.001
AW	20	7	0.820**	< 0.001
Z/r^2	20	8	-0.038	0.872
Z^2/r	20	8	0.024	0.921
Δ*IP*	20	9	0.271	0.248
Z^{*2}/r	20	9	0.469*	0.037
Z/*r*	20	9	0.025	0.916
Z/AR^2	20	9	0.220	0.352
Z/*AR*	20	9	0.230	0.329
IP	20	9	0.289	0.216
N	20	10	0.857**	< 0.001
*Z**	20	10	0.749**	< 0.001
X_m	20	10	0.760**	< 0.001
OX	20	11	0.178	0.453

* *Correlation is significant at the 0.05 level (2-tailed).*
** *Correlation is significant at the 0.01 level (2-tailed).*

Table 4 Results of correlation analysis among the eight selected metal ionic properties

		$\|\lg K_{OH}\|$	σ_p	ΔE_0	$X_m^2 r$	*AN*	Z^{*2}/r	*N*
R	*AR*/*AW*	0.445*	0.629**	0.482*	-0.424	-0.606**	-0.464*	-0.645**
	$\|\lg K_{OH}\|$		0.471*	0.428	-0.256	-0.407	-0.550*	-0.353
	σ_p			0.860**	-0.629**	-0.388	-0.759**	-0.860**
	ΔE_0				-0.676**	-0.247	-0.863**	-0.886**
	$X_m^2 r$					0.682**	0.442	0.816**
	AN						0.122	0.498*
	Z^{*2}/r							0.670**
sig. (2-tailed)	*AR*/*AW*	0.049	0.003	0.032	0.062	0.005	0.039	0.002
	$\|\lg K_{OH}\|$		0.036	0.060	0.277	0.075	0.012	0.127
	σ_p			＜0.001	0.003	0.091	＜0.001	＜0.001
	ΔE_0				0.001	0.294	＜0.001	＜0.001
	$X_m^2 r$					0.001	0.051	＜0.001
	AN						0.607	0.025
	Z^{*2}/r							0.001
N	*AR*/*AW*	20	20	20	20	20	20	20
	$\|\lg K_{OH}\|$		20	20	20	20	20	20
	σ_p			20	20	20	20	20
	ΔE_0				20	20	20	20
	$X_m^2 r$					20	20	20
	AN						20	20
	Z^{*2}/r							20

* *Correlation is significant at the 0.05 level (2-tailed).*
** *Correlation is significant at the 0.01 level (2-tailed).*

The eight metal ionic properties were transformed into eight components. PCs, with eigenvalue greater than or equal to 1,means they carry the majority of the information of the data, while the others with little information could be discarded [27].In the current study,PC_1 and PC_2have eigenvalues greater than 1(Fig. 2) and both these two PCs contain 77.40% of the information of the variances (Table 5).

PCs obtained by weighted linear combinations of the original variables were as follows:

$$PCs=as_1 stdx_1+as_2 stdx_2+\ldots+as_m stdx_m \quad (1)$$

Where $stdx_m$ refers to the transformed original variable, and as_m is the principal component score coefficient (Table 6)

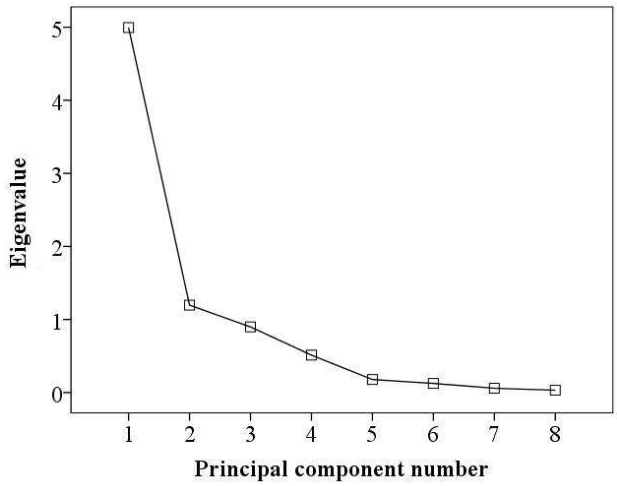

Fig.2 Eigenvalue of PCs

Table 5 Statistical information of PCs

Principal component	Extraction sums of squared loadings		
	Total	% of variance	Cumulative %
1	4.995	62.440	62.440
2	1.197	14.961	77.401
3	0.899	11.232	88.633
4	0.513	6.412	95.045
5	0.178	2.231	97.276
6	0.126	1.570	98.846
7	0.059	0.742	99.589
8	0.033	0.411	100.000

Table 6 PCs score coefficients matrix

Metal ionic properties	PCs	
	1	2
AR/*AW*	0.147	-0.249
$\|\lg K_{OH}\|$	0.118	0.006
σ_p	0.182	0.153
ΔE_0	0.179	0.304
$X_m^2 r$	-0.158	0.248
AN	-0.118	0.646
Z^{*2}/r	-0.159	-0.423
N	-0.187	-0.009

Multiple Linear Regression Analysis of PCs and TON

The multiple linear regression analysis, taking PC_1 and PC_2as independent variables and TON as the dependent variable, was performed. Goodness-of-fit test (adj. R^2=0.905, N=20) and *F* test (*sig*. <0.001), and the *t*-test (*sig*. < 0.001) in Table 7 show the model is statistically reliable. The multiple linear regression model is described by model (2). Using Model (2) and the PCs score coefficients in Table 6; we could obtain the QICAR model (3):

$$TON=-13.145PC_1+5.647PC_2+34.050 \quad (2)$$

$$TON=-70.675AR/AW-0.353|\lg K_{OH}|-28.312\sigma_p-0.537\Delta E_0 + 2.436X_m^2 r+ 0.240AN-0.024Z^{*2}/r+0.475N + 26.033 \quad (3)$$

The metal ionic properties$X_m^2 r$,*AN* and *N* have positive coefficients and play positive roles in the model, while the metal ionic properties *AR*/*AW*, $|\lg K_{OH}|$, σ_p, $\Delta E_0$and Z^{*2}/r have negative coefficients andnegatively influence the model.

Table 7*t*-test to PC_1 and PC_2

Model	Unstandardized coefficients		Standardized coefficients	*t*	*sig.*
	B	Std. error	Beta		
(constant)	34.050	1.032		33.002	< 0.001
PC_1	-13.145	1.059	-0.879	-12.417	< 0.001
PC_2	5.647	1.059	0.378	5.335	< 0.001

Comparison of Simulated Values with Observed Values

The Nash-Suttcliffe simulation efficiency coefficient (NSC) was selected to evaluate the accuracy of the QICAR model. NSC is the fraction of the variance in the observation explained by the model; a higher value indicates a more accurate model [28]. The formula for NSC is given as follows:

$$NSC = 1 - \frac{\sum_{i=1}^{n} (P_{exp} - P_{pre})^2}{\sum_{i=1}^{n} (P_{exp} - \overline{P}_{exp})^2} \quad (4)$$

Where P_{pre} refers to the simulated value, P_{exp} is the observed value, $\overline{P}_{exp}$ is the mean observed value.

In the current study, the twenty metal ions (Table 1) were used in building the QICAR model, and the other seven metal ions (Table 2) were used in testing the accuracy of the model. From Formula (4), the NSC for model building and model testing are 0.91 and 0.85 respectively. This means that the QICAR model can be well applied to predict the TON of the metal ions.

Comparison of Simulated Values with Experiment Data

The 15min EC_{50} for *photobacterium phosphoreum* of nine metal ions were obtained through experiment and normalization processing was carried out (Table 8).Correlation analysis between normalized EC_{50} and the corresponding simulated TON was performed. Table 9showsa highly significant correlation between them (*sig*. = 0.002).All the studies indicated that the TONs of the metal ions can be calculated by the QICAR model and correlated with other forms of toxicity data.

Table8Normalized EC_{50} and the corresponding simulated TONs of nine metal ions

Metal ions	Normalized EC_{50}	Simulated TON
Cd^{2+}	0.100006	45.3
Co^{2+}	0.100223	36.0
Cr^{3+}	0.100385	34.1
Cu^{2+}	0.100036	37.9
K^{+}	0.900000	18.8
Mn^{2+}	0.107343	32.2
Ni^{2+}	0.100000	37.4
Sr^{2+}	0.474140	28.8
Zn^{2+}	0.100004	38.7

Table 9 Correlation analysis between normalized EC_{50} and the corresponding simulated TON

	N	*R*	*sig.* (2-tailed)
normalized EC_{50}	9	-0.876^{**}	0.002

Sensitivity analysis

At first, taking Pb^{2+} as an example, sensitivity analysis of the eight metal ionic properties in the QICAR model was carried out to show which metal ionic properties have more impact on TON.

Keeping the other seven metal ionic properties constant, TON was recalculated when a metal ionic property changed by -20%, -10%, 10% and 20%. A sensitivity coefficient is basically the ratio of the change in output over the change in input [29].Table 10 shows the sensitivity coefficients of the eight metal ionic properties in the QICAR model. From the table, sensitivity analysis chart was drawn by taking the variable proportion as ordinate and the recalculated TON as abscissa (Fig.3).On the basis of the figure, it is evident that *AN* has the largest sensitivity coefficient and is the most critical factor affecting TON, and the impact degree of the other seven metal ionic properties on TON are $X_m^2 r$, N, σ_p, $|\lg K_{OH}|$, Z^{*2}/r, AR/AW and ΔE_0.

Then sensitivity coefficients of the remaining nineteen metal ions were obtained in the same way (Table 11).From the table, the impact degree of the eight metal ionic properties on TON is different for each metal ion. For a lot of metal ions (Ag^{+}, Ba^{2+}, Cd^{2+}, Cr^{3+}, Cs^{+}, Fe^{3+}, Hg^{2+}, La^{3+} andSr^{2+}),*AN* is still the most critical factor affecting TON. But for Co^{2+}, Cu^{2+}, Mn^{2+}, Ni^{2+} and Zn^{2+}, *N* is the most critical factor; for Ca^{2+}, K^{+}, Mg^{2+} and Na^{+},$\sigma_p$is the most critical factor; for Li^{+}, *AR*/*AW* is the most critical factor. About the strong impact of *AN* and *AR*/*AW* on TON, Li et al. has the similar finding[30]. σ_p separates metal ions into three groups: soft metal ions (for example, Ag, Cd and Hg), which prefer to bind to sulfur; hard metal ions (for example, Ba, Ca and Na), which prefer to bind to oxygen or nitrogen; borderline metal ions (for example, Co, Ni and Zn) [31]. And the soft metal ions are more toxic than the

hard metal ions because of the relative importance of metal ion binding to sulfur on biomolecules [12]. Zhang reported, in his study on the relationship between cation' structure and H_2S system analysis, the difference of polarization force in different cations depends largely on *N* [22]. And this may be the reason for the change of metal ion toxicity.

Table 10 Sensitivity coefficients of the eight metal ionic properties in the QICAR model for Pb^{2+}

Metal ionic properties	Variable proportion (%)	Recalculated TON	Sensitivity coefficient
AR/*AW*	-20	62.92	-0.525
	-10	62.87	
	+10	62.76	
	+20	62.71	
$\|\lg K_{OH}\|$	-20	63.44	-3.125
	-10	63.13	
	+10	62.50	
	+20	62.19	
σ_p	-20	63.56	-3.725
	-10	63.19	
	+10	62.44	
	+20	62.07	
ΔE_0	-20	62.83	-0.075
	-10	62.82	
	+10	62.81	
	+20	62.80	
$X_m^2 r$	-20	59.67	15.725
	-10	61.24	
	+10	64.39	
	+20	65.96	
AN	-20	58.88	19.675
	-10	60.85	
	+10	64.78	
	+20	66.75	
Z^{*2}/r	-20	62.96	-0.725
	-10	62.89	
	+10	62.74	
	+20	62.67	
N	-20	60.92	9.500
	-10	61.87	
	+10	63.77	
	+20	64.72	

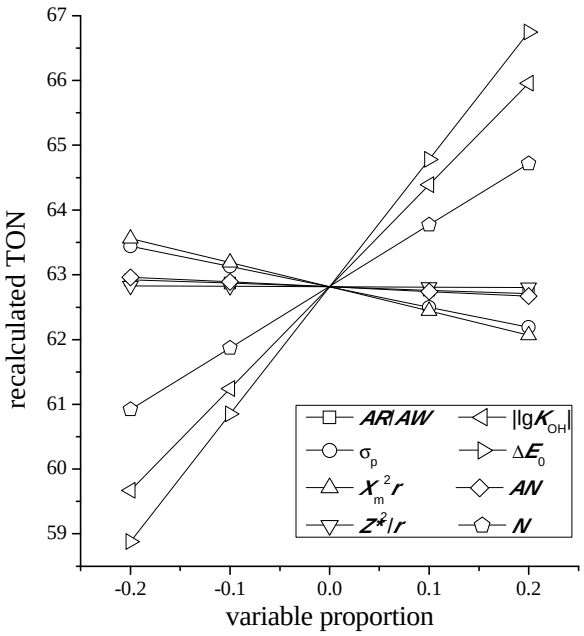

Fig.3 Sensitivity analysis chart for Pb^{2+}

Table 11Sensitivity coefficients of the eight metal ionic properties in the QICAR model for the remaining nineteen metal ions

metal ion properties	Ag^+	Ba^{2+}	Ca^{2+}	Cd^{2+}	Co^{2+}	Cr^{3+}	Cs^+	Cu^{2+}	Fe^{3+}	Hg^{2+}
AR/*AW*	-0.997	-1.117	-3.371	-0.933	-1.498	-1.696	-1.392	-1.498	-1.569	-0.523
$\|\lg K_{OH}\|$	-3.883	-4.730	-4.413	-3.424	-3.459	-1.306	0.000	-2.824	-0.777	-1.306
σ_p	-2.095	-5.181	**-5.124**	-2.293	-3.681	-3.029	-6.172	-2.944	-2.746	-1.840
ΔE_0	-0.430	-1.563	-1.541	-0.215	-0.150	-0.220	-1.627	-0.081	-0.413	-0.494
$X_m^2 r$	10.426	2.728	2.436	6.602	5.773	4.166	2.655	4.848	4.482	9.939
AN	**11.280**	**13.440**	4.800	**11.520**	6.480	**5.760**	**13.200**	6.960	**6.240**	**19.200**
Z^{*2}/r	-0.286	-0.173	-0.246	-0.558	-0.667	-0.837	-0.067	-0.681	-1.069	-0.520
N	8.550	3.800	3.800	8.550	**7.125**	5.225	3.800	**8.075**	6.175	8.550
metal ion properties	K^+	La^{3+}	Li^+	Mg^{2+}	Mn^{2+}	Na^+	Ni^{2+}	Sr^{2+}	Zn^{2+}	
AR/*AW*	-4.177	-0.954	**-15.478**	-4.509	-1.442	-5.718	-1.505	-1.668	-1.414	
$\|\lg K_{OH}\|$	-5.648	-3.177	-5.013	-4.024	-3.742	-5.224	-3.142	-4.589	-3.177	
σ_p	**-6.568**	-4.841	-6.993	**-4.728**	-3.539	**-5.974**	-3.567	-4.926	-3.256	
ΔE_0	-1.573	-1.278	-1.638	-1.273	-0.639	-1.455	-0.140	-1.557	-0.408	
$X_m^2 r$	2.485	3.410	1.778	3.021	3.922	2.144	6.066	2.777	5.895	
AN	4.560	**13.680**	0.720	2.880	6.000	2.640	6.720	**9.120**	7.200	
Z^{*2}/r	-0.077	-0.365	-0.053	-0.341	-0.559	-0.114	-0.673	-0.195	-0.716	
N	3.800	3.800	0.950	3.800	**6.175**	3.800	**7.600**	3.800	**8.550**	

CONCLUSION

Based on the whole analysis of the study, the following conclusions can be formed:
(1)The 22 metal ionic properties can be artificially divided into eleven groups by their ionic behavior: *AR*/*AW*; $|\lg K_{OH}|$; σ_p;*r*, *AR*; ΔE_0;$X_m^2 r$;*AN*/Δ*IP*, *AN*, *AW*;*Z*/r^2, Z^2/r; Δ*IP*, Z^{*2}/r, *Z*/*r*, *Z*/AR^2, *Z*/*AR*, *IP*;*N*, *Z**,X_m; *OX*.
(2) The QICAR model can be used to predict the TON of other unknown metal ions.
(3) The metal ionic properties$X_m^2 r$,*AN* and *N* play positive roles in the QICAR model, while the metal ionic properties *AR*/*AW*, $|\lg K_{OH}|$, σ_p, ΔE_0 and Z^{*2}/r have a negative influence on the QICAR model.
(4) The impact degree of the metal ionic properties in the QICAR model on TON is different for each metal ion. For Pb^{2+}, Ag^+, Ba^{2+}, Cd^{2+}, Cr^{3+}, Cs^+, Fe^{3+}, Hg^{2+}, La^{3+} and Sr^{2+}, *AN* is the most critical factor affecting TON; for Co^{2+}, Cu^{2+}, Mn^{2+}, Ni^{2+} and Zn^{2+}, *N* is the most critical factor; for Ca^{2+}, K^+, Mg^{2+} and Na^+, σ_p is the most critical factor; for Li^+, *AR*/*AW* is the most critical factor.

Acknowledgements
The research was supported by the Key Projects in the National Science & Technology Pillar Program in the Eleventh Five-Year Plan Period (2008BAC43B01).

REFERENCES

[1] C González-Maćias; ISchifter; DBLluch-Cota,*Environ.Monit.Assess.*,**2006**, 118(1-3),211-230.
[2] S Li; ZXu; X Cheng,*Environ. Geol*., **2008**,55(5),977-983.
[3] S Li; QZhang,J. *Hazard. Mater*.,**2010**,181(1-3), 482-488.
[4] NS Fisher,*Limnology and Oceanography*, **1986**, 31(2), 443-448.
[5] GL Turdean,*Int. J.Electrochem*., **2011**,115(71), 1-15.
[6] YLi;L Jiang;XLLi,*Chem. Res. Chi*nese U., **2013**, 29(3), 568-573.
[7] ZM Kong."EnvironmentalToxicology (3rd Edition)",Publishing House of Nanjing University, Nanjing,**2004**.
[8] SS Zamil;S Ahmad; MH Choi,*Bioresour. Technol*., **2009**, 100(6), 1895-1902.
[9] MCNewman; JT McCloskey; CPTatara,Environ. *Health Perspect*.,**1998**,106(6), 1263-1270.
[10] DROwnby; MCNewman,*QSAR Comb. Sci*.,**2003**,22(2), 241-246.
[11] CPTatara; MC Newman; JT McCloskey,*Aquat.Toxicol*.,**1998**,42(4), 1419-1426.
[12] JTMccloskey; MC Newman; SBClark,*Environ.Toxicol. Chem*., **1996**,15(10), 275-281.
[13] HTWolterbeek; TGVerburg,*Sci. Total Environ*.,**2001**,279(1-3), 87-115.
[14] KLE Kaiser,*J. Fish. Aquat. Sci*.,**1980**,37(2), 211-218.
[15] L Kaufman; PJRousseeuw,"Finding groups in data: an introduction to cluster analysis",John Wiley& Sons, lnc.,Hoboke,**1990**.
[16] T Velmurugan; TSanthanam,*Inf. Technol. J*., **2011**, 10(3), 478-483.
[17] AJScott;MKnott,*Biometrics*, **1974**,30(3), 507-512.
[18] HHBock,*Comput. Stat. Data Anal.*, **1996**,23(1), 1497-1503.
[19] CJKrebs."Ecological methodology (2nd edition)",Addison Wesley Longman, lnc., California,**1999**.
[20] HB Zhu."AppliedStatistics and SPSS Application",Publishing House of Electronics Industry, Beijing,**2011**.
[21] XHYang;CSYin,*Chinese J.Inorg. Chem.*, **2004**,20(11), 785-788.
[22] YTZhang;SLXiao,*Journal of Sichuan Normal Univ*., **1989**, 10(4), 315-319.
[23] RGPearson; RJMawby,"Halogen Chemistry", ed. V.Gutmann,Academic Press,London,**1976**, 55-85.

[24] HAbdi; LJWilliams.Wiley *Interdisciplinary Review*, 2, **2010**.
[25] EBorgonovo,*Reliab. Eng. Syst. Safe.*, **2007**, 92(6), 1458-1467.
[26] CH Yu."SPSS and StatisticalAnalysis", Publishing House of Electronics Industry, Beijing,**2006**.
[27] ITJolliffe."Principal Component Analysis,Second Edition", Springer series in statistics, New York,**2002**.
[28]XX Yu; XM Zhang; LLNiu,*Int. J. Sediment Res.*, **2009**,24(4), 245-257.
[29] DMHamby,*Environ.Monit.Assess*.,**1994**,32(2), 135-154.
[30] YLi; XLLi; XY Du,*Hum. Ecol. Risk Assess*.,**2012**,18(6),315-320.
[31] MMJones; WK Vaughn,*J. Inorg.Nucl.Chem*.,**1978**,40(12), 2081-2088.