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Metal Ions' Ecotoxicity – QSAR Study

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Abstract: Quantitative structure activity relationships (QSARs) were developed to predict ecotoxicity of divalent metal ions by correlating the biological activity, $A=\log(1/EC_{50})$, values with two ion descriptors, chosen to represent the binding tendencies of metals to ligands, the first hydrolysis constant (K_{OH}) and the electronegativity coefficient (χ). Relative metal ions' ecotoxicity (Ca^{2+}, Ba^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Sr^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+} and Zn^{2+}) was predicted with regression models. The models are compared with other based on electronic effects towards emphasizing different roles they assign in ecotoxicity molecular mechanisms.

Keywords: eco-toxicity, the first constant of hydrolysis, lethal dose, Hansch factors.

1. Introduction

Metal toxicity is largely determined by the functional ionic selectivity of proteins (complexation, coordination, chelation, ion exchange, adsorption). The QSARs methods offered a new way to explore the interaction between the absorbed metal ions and the functional groups on the biomass [1]. Metals can cause toxicity at the cellular level [2] in higher plants by affecting membrane permeability, by inhibiting, inducing or increasing the activity of enzymes and by activating defense mechanisms against increased metal phytotoxicity.

Approximately two-thirds of the elements in the periodic table can be categorized as metals. Besides luster, malleability, and conductivity, one of the fundamental characteristics of metals is their low ionization potential. As a result, the ionic forms of these elements predominate in the biosphere.

Considering the diverse properties of these ions, it is not surprising that through the process of evolution, metal ions have been co-opted into numerous roles in biology. Metal ions are required for so many biochemical reactions that it is likely that they also had an important role in the RNA world.

The direct prediction of properties is in general not feasible either owing to lack of computing resources or lack of knowledge about the relationship between structure and property. QSAR predictions for inorganic toxicity (especially for the toxicity of metal ions), however, are less developed. In the year 2000, a paper entitled, "QSARs for metals - fact or fiction?", by Walker and Hickey [3] raised a number of issues.

2. Experimental

In predictive toxicology, we exploit the toxicological knowledge about a set of chemical compounds in order to predict the degree of activity of other compounds [4]. More specifically, we mathematically model the relationship between specific properties of training compounds (i.e. compounds for which the degree of activity is known) and their toxicological activity and apply the model to query compounds (i.e. compounds for which the degree of activity is not known) to obtain predicted activities.

The process of model-building is called (Quantitative) Structure Activity Relationship ((Q)SAR). SARs are models based on structural features, and QSARs rely on quantitative (frequently physico-chemical) properties. The most general mathematical form of a (Q)SAR is:

Activity = f(physicochemical and/or structural features)

Multilinear models have been in use since a long time. As linear equations, they are easy to use and relatively straightforward to interpret. For n instances they are defined as the coefficients that minimize the error on a system of n linear equations [5 - 8]:

$$y_i = b_1 x_{i1} + b_2 x_{i2} + ... + b_m x_{im} + d \qquad i \in \{1, ..., n\}$$

where b and d are the coefficients to learn.

Relationships were developed to correlate a structural parameter (i.e.,acidity) with activity. In some cases, the mono-parametric relationships correlating structure with activity were adopted with the form:

^Paper from the *The XIVth International Symposium „YOUNG PEOPLE AND MULTIDISCIPLINARY RESEARCH"*, Timisoara, 2012

$$A = \log(\frac{1}{C}) = a + b \log pK_a$$

where C is the molar concentration of compound that produces a standard response (e.g., LD_{50}, EC_{50}).

Ion characteristics of inorganic species can be used to predict the relative toxicity or sublethal effects of metal ions. Many of these characteristics reflect the binding tendencies of metals to ligands. For example, *electronegativity* (χ) is correlated with the energy of an empty valence orbital and reflects the ability of a metal to accept electrons, combining electronegativity with the ionic radius yields an index that quantifies the importance of covalent interactions relative to ionic interactions [9]; the *acidity of metal ions pKa* like $|\log K_{OH}|$, where K_{OH} is the first hydrolysis constant:

$$[M(H_2O)_n]^{x+} + HOH \rightarrow [M(H_2O)_{n-1}OH]^{(x-1)+} + H_3O^+$$

(metal ions in aqueous solution behave as Lewis acids). The relationship between pK_a and some biological responses was often inverse parabolic, in which a maximum in the biological response occurred at some optimum pK_a value:

$$A = \log(\frac{1}{C}) = a + bpK_a + c(pK_a)^2$$

The objective of this study was to establish the relationship between the metal ionic properties with their biological activity (median effect concentration EC_{50}) using QSAR model based on trial and test set of 12 divalent metal ions, to improve the QSAR predictive model and to implore the understanding of the metal–(eco)toxicity correlation.

Nevertheless, many efforts have been focused on applying QSAR methods to non-linearity features from where the "expert systems" emerged as formalized computer-based environments, involving knowledge-based, rule-based or hybrid automata able to provide rational predictions about properties of biological activity of chemicals or of their fragments; it results in various QSAR based databases: the model database (QMDB) - inventorying the robust summaries of QSARs that can be appealed by envisaged endpoint or chemical, the prediction database (QPDB) - when data from QMDB are used for further prediction to be stored, or together towering the chemical category database (CCD) documentation [5, 7, 10 - 12].

Ion characteristics used for modeling (Table 1) were obtained from a variety of sources. The first hydrolysis constants (log K_{OH}) were obtained from Baes and Mesmer [13] and Brown and Allison [14] and and average electronegativity values (χ) were taken directly from Allred [15]. The median effect concentration values (EC_{50}) were taken from John T. McCloskey [16].

TABLE 1. Metal ion characteristics and biological activity (A^{obs}) used in regression models, trial (Gaussian) and test (Nongaussian) sets

Type	Metal Ions	EC_{50} (μM/L)	$A^{obs}=\|\log(EC_{50})\|$	χ	$pKa=\|\log K_{OH}\|$
G1	Mn^{2+}	1.571	0.196176	1.55	10.6
G2	Cd^{2+}	27.000	1.431364	1.69	11.7
G3	Mg^{2+}	87.242	1.940726	1.31	11.42
G4	Ni^{2+}	566.000	2.752816	1.91	9.86
G5	Co^{2+}	874.000	2.941511	1.88	9.65
G6	Ba^{2+}	95.455	1.979799	0.89	13.82
G7	Zn^{2+}	35.000	1.544068	1.65	9.60
G8	Cu^{2+}	1.620	0.209515	1.90	8.96
NG1	Sr^{2+}	235.527	2.372041	0.95	13.18
NG2	Hg^{2+}	0.919	0.03668	2.00	3.40
NG3	Ca^{2+}	94.702	1.976359	1.00	12.7
NG4	Pb^{2+}	1.150	0.060698	2.33	7.80

3. Results and Discussion

In the Table 1 were obtained some data for the series of ions metal, the median effect concentration values (EC_{50}), from literature data [15], among the employed activity $A=\log_{10}(EC_{50})$ and structural parameters as *electronegativity* (χ) and the *acidity of metal ions pKa* like $|\log K_{OH}|$.

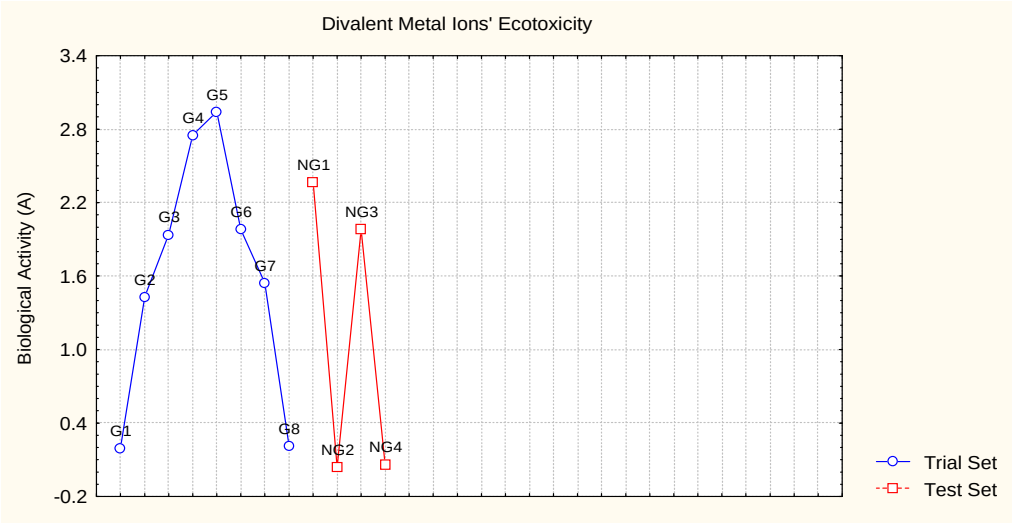

Figure 1. The plot of the divalent metal ions' EC_{50} toxicities of Table I (classification as Gaussian (G) or non-Gaussian (NG) for being employed for the trial and test QSAR sets, respectively).

TABLE 2. Structure activity relationships for the "Trial set" (8 metal ions) of Table 1

No.	Model	R	SEE
1.	$A^{obs} = 0.6935 + 0.0869\ pK_a$	0.1337	1.0946
2.	$A^{obs} = -1.7267 + 0.5213\ pK_a - 0.0190\ pK_a^2$	0.1409	1.1879
3.	$A^{obs} = 7.8591 - 9.3759\ \chi + 3.2867\ \chi^2$	0.3575	1.1300
4.	$A^{obs} = -5.3382 + 0.4781\ pK_a + 0.6939\ \chi^2$	0.3540	1.1316
5.	$A^{obs} = -39.1408 + 13.8270\ pK_a - 0.6350\ pK_a^2 - 45.5479\ \chi + 14.9044\ \chi^2$	0.7201	1.0849

TABLE 3. Observed and predicted activity relationships for the "Test set" ions metal of Table 1 using models equations (1 to 5) from Table 2.

Metal Ions	A observed	A predicted				
		Model 1	Model 2	Model 3	Model 4	Model 5
Sr^{2+}	2.372041	1.838842	1.843498	1.918242	1.589403	2.972402
Hg^{2+}	0.03668	0.98896	-0.17392	2.2541	-0.93706	-30.9478
Ca^{2+}	1.976359	1.79713	1.8293	1.7699	1.42757	3.39945
Pb^{2+}	0.060698	1.37132	1.18348	3.856419	2.158094	4.86429
	R	0.9206	0.8096	0.7089	0.3895	0.5402
	SEE	0.5919	0.8896	1.0692	1.3962	1.2757

Since the usual statistic analysis demands the *trial* and *test* stages in validation the metal ions of Table 1 were classified accordingly based on the best fulfillment of the normal distribution of input data (EC_{50}), as evidenced from Figure 1, however, such that each category of ions metal to be represented in both "trial" and "test" sets of toxicants.

We obtained some data (structure activity relationships) for all possible correlation models considered from the data in Table I together with the statistical (simple correlation factor, standard error of estimation SEE). The results are in the table 2.

We see the Table 2 and we obtain useful information about the structure parameters in correlation with electronegativity, acidity and biological activity. For the metal ions serie the maximum of R (R = 0.72) and the lowest SEE tells us that the model $A = f(pK_a, pK_a^2, \chi, \chi^2)$ is predicted as the most reliable one across the A models of Table 2. The two-variable model using pK_a and χ^2 provided the modest overall model among the total ion A values as judged by the lowest SEE value and R value.

The significant relationship indicates that the toxicity of all series of ions metal can be best described if the descriptors pK_a, pK_a^2 χ, and χ^2 are included together in a factorial regression model. The toxicity (EC_{50}) of the series of ions metal could be described best by a multilinear regression model including the acidity and the electronegativity. Fair agreement between experimental data and model computation is achieved using the first model as expressed in Table 2 shows the relationship of the predicted toxicity values with the observed ones for the best correlation coefficient found (R = 0,7201), i.e. the model 5.

However, one may note from the Table 3 that the predicted correlation for this best trial – the model 1 corresponds with a relatively good prediction for the test compounds; instead the trial-model 5 in Table 2 with a modest correlation about R = 72.01 % provides the predicted-tested correlation in Table 3 about R = 54.02 % even lesser that its trial counterpart. Generally, two-variable models provided better fits than one-variable models. These predictive models, if developed, could prove very useful in areas where data on metal toxicity or sublethal effects are lacking or incomplete. Once a model has been developed with representative metals for a particular organism under certain environmental conditions, the relative effect of additional metals could be predicted.

The present analysis enlighten on the fact the parabolic dependence on activity respecting the acidity and electronegativity seems to be the most preferred (selected) model for higher prediction based on a collection of QSAR trial equation; this, perhaps, it features at the best the increase and decrease (according with a parabolic shape) of the compound action into the organism as reflected into the activity response, respectively.

4. Conclusion

Our results (models of metal ions' (eco) toxicity using ion characteristics) agree with the target theory respecting the increase and decrease of the electrical and electronic effects of a toxicant as reflected into its organism activity. Actually, for a group of divalent metal ions, the so called Trial set of compounds found to display the first selection/screening in causing natural bioactivity was show to provide somehow reversed behavior in correlation output for the tested or Test set of ions metal, with the best response related with the parabolic dependency of the activity by means of the chemical transport index of electronegativity and first constant of hydrolysis. Such behavior is susceptible for further generalization and will be studied and will be necessary to determine their range of applicability and reported in the subsequent communications.

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