QSAR STUDIES FOR PREDITION OF CATION TOXICITY

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ABSTRACT

The quantitative structure-activity relationship approach used for modeling and predictions of variety biological/toxic effects is mainly applied for investigation of organic compounds. However, the approach could be also successfully used in cases where the toxic response should be predicted for inorganic chemicals. While molecules of organic compounds reflect their properties as a whole, the inorganic compounds dissociate in various degrees and the properties have to be thus attributed to anions, cations, or undissociated molecules. Depending of each specific case different descriptors could be used for modeling and further screening of chemicals of interest. The aim of this study is to present some examples for QSAR applications used for prediction of cation toxicity.

***Keywords**: toxicity of inorganics, computational toxicology, QSAR*

INTRODUCTION

According to the quantitative structure-activity relationship (QSAR) paradigm, if the molecular parameters (known as molecular descriptors) have been calculated for a group of compounds, but experimental data on the activity of those compounds are available for only part of the group, it is possible to interpolate the unknown activity of the other compounds from the molecular descriptors using a suitable mathematical model. Depending on the type of experimental data, QSAR can predict the physical and chemical properties or a vast range of activities and toxic influences of new compounds [1-4]

Although the QSAR is a widely used approach for organic compounds, application of predictive models to inorganic toxicants (e.g., metals) is poorly represented in the environmental and health toxicology literature. A mathematical equation that relates metal toxicity to ion characteristics of metals would be useful to toxicologists for predicting intermetal trends in bioactivity. The number of metals of environmental concern is small in comparison to the number of toxic organic chemicals. This, however, does not diminish the utility of predictive models for metals. The toxic response of different organisms, the chemistry of different exposure media and the duration of exposure combine to produce thousands of situations where metals would have unique and different toxicities [5, 6].

The aim of this study is to present some examples for QSAR applications used for prediction of cation toxicity.

Molecular descriptors used in prediction of metal toxicity

In the absence of precise information regarding the biological mechanisms that contribute to the production of the biological activity, and in the absence of satisfactory information regarding the state of the metal ions in biological environments, a suitable QSAR approach would be to choose descriptors that represent the long path that the metal ions have to travel up to the biological target [7]. The choice of descriptors must consider all the physical–chemical processes that happen to the metal ion or metal compound up to the last event, which is the interaction with the biological target. Correspondingly, a good correlation of metal biological activity with descriptors depends on a better understanding of the physicochemical or biological mechanisms in which metal ions participate in biological environments. Many descriptors that can be used for metals are generally common to chemical structures—for example, molar refractivity, electronegativity, and so on. Other descriptors are specific for metals or metal ions, depending on their electronic configuration and their position in the periodic table. A review of the parameters found in the literature to

correlate with metal toxicity shows the use of atomic parameters such as atomic radii and the ionization energies; the use of basic chemical properties such as the valence; the electrochemical character and thermodynamic measures that describe the electrochemical reactions of the metals; the theory of hard and soft acids and bases; and properties of the metal compounds, for example, the solubility of metal compounds or other particularities of the metal compounds [8].

Approaches for prediction metal toxicity

While there is abundant information and understanding of mechanisms by which foreign organic chemicals affect biological systems a little is known about the toxic potential of inorganic chemicals which can be used for QSAR modeling purposes. In attempting to extend the above considerations to metal compounds [9], it is of great importance to get more details for physiological functioning of metals in biological systems. In this respect, it will be very important if biochemical toxicology of organic and inorganic chemicals could be explained by similar key chemical properties or processes that may be common to both groups.

Recent studies [10] using metal-ligand binding characteristics to predict metal toxicity and the development of quantitative ion character-activity relationships (QICARs) are showing promise as a screening approach and in situations analogous to those in which QSARs are being applied. Since the major focus in pharmacology and to a large extent in human toxicology has been on organic drugs and poisons, QICARs have not been well developed. In addition, chemical speciation complicates prediction because several metal species usually are present simultaneously and the bioavailability of each is ambiguous.

Inter-metal trends in toxicity were successfully modeled with ion characteristics reflecting metal binding to ligands associated with a wide range of effects. In general, models for metals with the same valence (i.e., divalent metals) were better than those combining mono-, di-, and trivalent metals. Ion characteristics that were most useful in QICAR model construction included the softness parameter and absolute value of the log of the first hydrolysis constant. The softness index quantifies the ability of the metal ion to accept an electron during interaction with a ligand. It reflects the importance of covalent interactions relative to electrostatic interactions in determining inter-metal trends in bioactivity. Interestingly, softness or molecular polarizability is often an important factor in molecular recognition and binding processes for organic compounds. The hydrolysis constant reflects the tendency for a metal ion to form a stable complex with intermediate ligands such as O donor atoms in biomolecules. There is not a clear counterpart for this on the organic chemical side, and it appears to be a distinctive feature that can be important in determining the relative bioactivity of metals.

There are several resolvable issues that need further attention before the QICAR approach has the same general usefulness as the QSAR approach. These issues include development and testing of more explanatory variables, careful evaluation of ionic qualities used to calculate explanatory variables, better understanding of models capable of predicting effects for widely differing metals (e.g., metals of different valence states), effective inclusion of chemical speciation, examination of more effects, and assessment of the applicability of QICARs to complex phases such as sediments, soils, and food.

Studies for prediction of metal toxicity and biosorbtion by QSARs

Cation toxicity to Vibrio fischeri, Daphnia magna, and Leuciscus idus melanotus

Acute aquatic toxicities of neutral inorganic species were estimated for three species using existing linear solvation energy relationship (LSER) equations developed for neutral organic compounds. Use of the whole inorganic species addresses ionic charge and elemental valence. The general LSER equation is

$$\text{Log(Property)} = mV_i/100 + s\pi^* + b\beta_m + a\alpha_m$$

where V_i is the intrinsic (van der Waals) molecular volume, π^* is the solute ability to stabilize a neighboring charge or dipole by nonspecific dielectric interactions, and β_m and α_m are the solute ability to accept or donate a hydrogen in a hydrogen bond. The coefficients m, s, b, and a are constants for a particular set of conditions, determined by multiple linear regression of the LSER variable values for a series of chemicals with the measured value for a particular chemical property [11].

Germination of sunflower seeds

Quantitative cationic activity relationships were developed to predict the toxicity of metal ions from physicochemical properties and natural occurrence levels [12]. In vivo toxicity data for different concentrations of nitrate salts of 17 metal ions ($Ag^{1+,}$ Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{3+}, K^{1+}, La^{3+}, Li^{1+}, Mg^{2+}, Mn^{2+}, Na^{1+}, Ni^{2+}, Pb^{2+} and Zn^{2+}) were developed based on germination of sunflower seeds in distilled water. The EC50 data were reported as the concentration giving 50% inhibition of radicle growth one day after emergence. Stepwise regression of the toxicity data produced correlations with some physicochemical properties and natural occurrence levels. For physicochemical properties, good results were obtained with the density of the elements, enthalpy of formation of metal sulfides, and the stability constants of metal ions with sulfate (r^2adj. = 0.72−0.81). For natural occurrence levels, good results were obtained with metal concentrations in soil, the median elemental composition of soils and the calculated mean of the elemental content in land plants (r^2adj. = 0.69 – 0.83).

Metal ions toxicity to planktonic and biofilm cells

The toxicity of 44 metals [13] to the biofilms and planktonic cells of Pseudomonas fluorescens was measured and expressed as minimum inhibitory concentration, minimum bactericidal concentration, and minimum biofilm eradication concentration. Linear regression analyses were conducted to determine the relationships between the measured toxicity values and the following physicochemical parameters: standard reduction-oxidation potential, electronegativity, the solubility product of the corresponding metal–sulfide complex, the Pearson softness index, electron density, and the covalent index. Each of the physicochemical parameters was significantly ($P < 0.05$) correlated with one or more of the toxicity measurements. Heavy metal ions were found to show the strongest correlations between toxicity and physicochemical parameters.

Predictive models for biosorbtion of various toxic metals

Quantitative cationic activity relationships was used for correlating metal ionic properties with maximum biosorption capacity (q_{max}) [14]. Heat inactivated biomass of Staphylococcus saprophyticus BMSZ711 was studied for biosorption of nine metal ions. Influence of contact time and initial pH was evaluated. q_{max} was determined by Langmuir isotherm. q_{max} values were modeled with 20 metal ionic characteristics. Classification of metal ions according to valence or soft/hard improved QICARs modeling and more characteristics significantly correlated with q_{max} which revealed that covalent bonding played major role in biosorption of soft metal ions and ionic bonding for borderline and hard ions.

Another study for metal ion biosorptive capacity [15] was established using QSAR models based on the classification of metal ions (soft, hard, and borderline ions). Ten kinds of metal were selected and the waste biomass of Saccharomyces cerevisiae obtained from a local brewery was used as biosorbent. Eighteen parameters of physiochemical characteristics of metal ions were selected and correlated with q_{max}. The suggestion was made that classification of metal ions could

improve the QSAR models and different characteristics were significant in correlating with q_{max}, such as polarizing power Z^2/r or the first hydrolysis constant $\log K_{OH}$ or ionization potential.

CONCLUSIONS

QSAR is an extremely multi-disciplinary field, potentially applicable to a wide range of problems and endpoints. In the environmental and human health area, there have been a number of applications for pollution prevention, toxicity screening, and risk assessment. Although such broad application potential is desirable and useful, it has also increased the opportunity for the misuse of such methods and approaches.

While the main focus is set on development of models for prediction the toxicological potential of organic compounds there is also urgent need for development of models that can help toxicologist in prediction of toxic potential of inorganic chemicals. Metal toxicity is largely determined by the functional ionic selectivity of proteins (complexation, coordination, chelation, ion exchange, adsorption). In this respect QSARs methods offered a way to explore the interaction between metal ions and the functional groups in biomolecules. Metals can cause toxicity by various mechanisms which require exhaustive analysis for identification of the appropriate molecular descriptors which could be used for development of scientific robust and reliable models.

In addition, despite of the good performance of the available models for metal toxicity one should point out that these models usually cannot be found as tools incorporated in currently most popular in silico platforms for QSAR analysis. In this respect systemic prioritization of most important toxic effects caused by inorganic compounds should be discussed. Ultimately, the incorporation of such models in non-commercial software tools (e.g. QSAR Toolbox) will be the fastest way for toxicological assessment of large number of potential inorganic toxicants.

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