# Predicting Water Quality Criteria for Protecting Aquatic Life from Physicochemical Properties of Metals or Metalloids

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Ⓢ *Supporting Information*

**ABSTRACT:** Metals are widely distributed pollutants in water and can have detrimental effects on some aquatic life and humans. Over the past few decades, the United States Environmental Protection Agency (U.S. EPA) has published a series of criteria guidelines, which contain specific criteria maximum concentrations (CMCs) for 10 metals. However, CMCs for other metals are still lacking because of financial, practical, or ethical restrictions on toxicity testing. Herein, a quantitative structure activity relationship (QSAR) method was used to develop a set of predictive relationships, based on physical and chemical characteristics of metals, and predict acute toxicities of each species for five phyla and eight families of organisms for 25 metals or metalloids. In addition, species sensitivity distributions (SSDs) were developed as independent methods for determining predictive CMCs. The quantitative ion character–activity relationships (QICAR) analysis showed that the softness index ($\sigma$p), maximum complex stability constants ($\log -\beta_n$), electrochemical potential ($\Delta E_0$), and covalent index ($X_m^2 r$) were the minimum set of structure parameters required to predict toxicity of metals to eight families of representative organisms. Predicted CMCs for 10 metals are in reasonable agreement with those recommended previously by U.S. EPA within a difference of 1.5 orders of magnitude. CMCs were significantly related to $\sigma$p ($r^2 = 0.76$, $P = 7.02 \times 10^{-9}$) and $\log -\beta_n$ ($r^2 = 0.73$, $P = 3.88 \times 10^{-8}$). The novel QICAR-SSD model reported here is a rapid, cost-effective, and reasonably accurate method, which can provide a beneficial supplement to existing methodologies for developing preliminarily screen level toxicities or criteria for metals, for which little or no relevant information on the toxicity to particular classes of aquatic organisms exists.
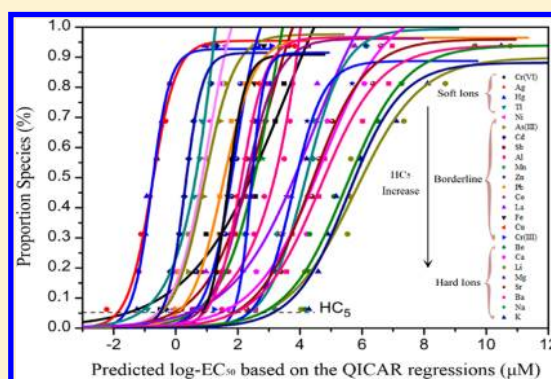
## INTRODUCTION

Metals can become contaminants in aquatic environments. The water quality criteria (WQC) for some metals were developed in the middle of the 20th century. Some acute toxicity data for aquatic organisms were used as the scientific basis for development of WQC and also for use in the environmental management.[1,2] To sustain the reproduction and survival of aquatic organisms, in 1976, the United States Environmental Protection Agency (U.S. EPA) published the first WQC guideline commonly referred to as the "Red Book", which recommended WQC for 12 metals or metalloids. Currently 167 ambient WQC for priority and nonpriority toxicants have been developed, and these WQC have been updated seven times.[3−9] However, there are only 12 aquatic life criteria values for priority metals and 4 criteria values for nonpriority metals in the latest water quality guideline,[9] in which specific criteria maximum concentrations (CMCs) are recommended for 10 metals. The CMCs for other metals are still lacking. This deficiency limits the capacities of assessing water quality and dealing with unexpected environmental incidents, pollution control and environmental risk management. The present CMCs were mainly derived from standardized aquatic life toxicity tests. Thus, environmental behavior in specific ambient media and different end points could lead to differences in toxicity of metals.[10] Comprehensive toxicity tests are time-

**Table 1. Two-Variable Regression Models Based on Seven Characteristics for Metal Ions[a]**

| species | phyla | predicting equations | $r^2$ | RSS | RMSE | F | P |
|---|---|---|---|---|---|---|---|
| *Chironomus tentans* | Arthropoda | $\log 48\ h - EC_{50} = (28.136 \pm 18.459)\sigma p + (-0.150 \pm 0.112)\log -\beta_n + (0.814 \pm 3.625)$ | 0.769 | 3.749 | 0.790 | 9.98 | 0.012 |
| *Crangonyx pseudogracilis* | Arthropoda | $\log 96\ h - LC_{50} = (39.716 \pm 25.627)\sigma p + (-0.254 \pm 0.136)\log -\beta_n + (1.678 \pm 4.533)$ | 0.791 | 8.520 | 1.103 | 13.26 | 0.004 |
| *Daphnia magna* | Arthropoda | $\log 48\ h - EC_{50} = (-0.272 \pm 18.674)\sigma p + (-0.360 \pm 0.136)\log -\beta_n + (6.604 \pm 4.093)$ | 0.869 | 1.360 | 0.583 | 13.25 | 0.017 |
| *Lymnaea acuminata* | Mollusca | $\log 96\ h - EC_{50} = (-2.160 \pm 0.821)X_m^2 r + (0.237 \pm 0.222)\ AN/\Delta IP + (5.557 \pm 1.399)$ | 0.827 | 1.453 | 0.696 | 7.191 | 0.070 |
| *Cyprinus carpio* | Chordata | $\log 96\ h - LC_{50} = (33.441 \pm 6.256)\sigma p + (0.412 \pm 0.137)Z/r + (-3.159 \pm 0.559)$ | 0.960 | 0.226 | 0.274 | 35.55 | 0.008 |
| *Brachionus calyciflorus* | Rotifera | $\log 24\ h - LC_{50} = (-0.297 \pm 0.082)\log -\beta_n + (-0.111 \pm 0.106)|\log K_{OH}| + (6.375 \pm 2.058)$ | 0.823 | 1.478 | 0.702 | 6.97 | 0.070 |
| *Bufo melanostictus* | Chordata | $\log 96\ h - LC_{50} = (6.955 \pm 20.353)\sigma p + (-1.569 \pm 0.474)X_m^2 r + (5.014 \pm 3.156)$ | 0.902 | 1.814 | 0.673 | 18.35 | 0.009 |
| *Lemna minor* | Angiosperms | $\log 96\ h - EC_{50} = (24.984 \pm 9.959)\sigma p + (1.494 \pm 0.439)\Delta E_0 + (-2.046 \pm 1.140)$ | 0.824 | 0.728 | 0.427 | 9.40 | 0.030 |

[a]$r^2$ is the coefficient of determination, RSS is the residual sum of squares, RMSE is root mean square deviation, and $p$ is the statistical significance level.

consuming and expensive, and testing on some endangered species cannot be conducted due to eco-ethics challenges. For other species, sometimes it is not possible to conduct controlled laboratory tests because of size, lack of information on culturing or maintaining them under laboratory conditions. Therefore, the importance of establishing a system to estimate CMCs that is based on limited toxicity test data is recognized. One of the commonly used models to predict criteria of metals is the recently developed biotic ligand model (BLM).[11−15] The U.S. EPA adopted the copper BLM for establishing WQC and extended the use of the BLM to WQC of silver and zinc.[16,17] The European Union also recently applied the BLM to assess chronic toxicity of nickel (Ni) and developed WQC for Ni.[18] The BLM is used to estimate the bioavailable fraction of metals for ascertaining the role of water chemistry on toxicity of metals to aquatic organisms. A model, based only on physicochemical properties to predict toxicity, has also been developed.[19] However, that model was of limited scope.

Quantitative structure activity relationships (QSARs) establish intrinsic relationships between characteristics of a compound to bioactivity or toxicity of metals by use of statistical analysis. Most QSARs have been developed for organic chemicals, with inorganic chemicals, such as metals being under-represented in the environmental toxicology literature.[20−22] Because of metal speciation, complexation, interactions in biological systems and formation/degradation of metal−ligand bond, correlation of toxicity with physical or chemical properties of metals is still challenging. It is known that most metals exist in biological system as cations and toxicity of metals depends mainly on cationic activity.[23] At present, ion characteristics have been used to predict toxicity or sublethal effects of metal ions, and the quantitative ion character−activity relationships (QICAR) models based on metal−ligand binding have recently been developed.[19,23−28] More than twenty ion characteristics including hydrolysis, ionization, covalent binding and spatial characteristics were used in a study conducted by Walker et al.,[29] to predict binding of soft ligands. However, there are still challenging issues to solve. First, existing QICAR models contained different metal toxicity data, which varied largely in exposure times, organisms, effects and effect levels. Second, most of QICAR models relate certain ion characteristics with toxicity of metals. Thus, novel characteristics of metals or metalloids could also be considered

and predictive relationships could be developed for additional aquatic species. The purpose of this study was to relate characteristics of data-rich metal ions with metal toxicities of each species of several representative aquatic organisms that were necessary for getting WQC, to predict the toxicities of additional data-poor metals and ultimately to obtain the CMCs for these additional metals.

The species sensitivity distribution (SSD) analysis is a promising method to determine CMCs, based on cumulative probability distributions of toxicity values for multiple species. For derivation of CMCs, the concentration of a chemical that can be used as a hazard level can be extrapolated from a SSD such that 95% of species would not be affected by a particular concentration of a specific metal.[30] The SSD can be used to estimate the concentration at which 5% of species would be affected. The concentration associated with the fifth percentile has been referred to as the 5% hazard concentration (HC$_5$). In the semiprobabilistic approach developed by Stephan,[31] the minimum data set required for derivation of a WQC for freshwater was at least three phyla and eight different taxonomic families.[32,33] As a result, the diversity and the sensitivities of a range of aquatic life are represented in the criteria values in order to estimate a concentration to protect organisms against small effects. The present study was conducted to compile the relative toxicity data of 25 metals or metalloids and to examine the relationships between selected physicochemical parameters and corresponding toxicities (LC$_{50}$ or EC$_{50}$) in eight families of representative organisms. This information was used to determine CMCs of each metal by SSD analysis and obtain a predictive relationship for CMCs.

## ■ MATERIALS AND METHODS

**Modeling Data Sets.** Toxicity data used in the present study were selected based on data collection and requirement described in 1985 U.S. EPA WQC guidelines where minimum eight species (three phyla) were required.[31] Those data have also been used in conjunction with metal criteria derivation and recent risk assessment.[34,35] For better comparison and consistence, toxicity data were further selected based on the following standards: (1) Toxicities of metals to each species were required from the same data source and the same research team under the same experimental conditions. (2) Results for six or more metals were investigated for each species. (3) Data
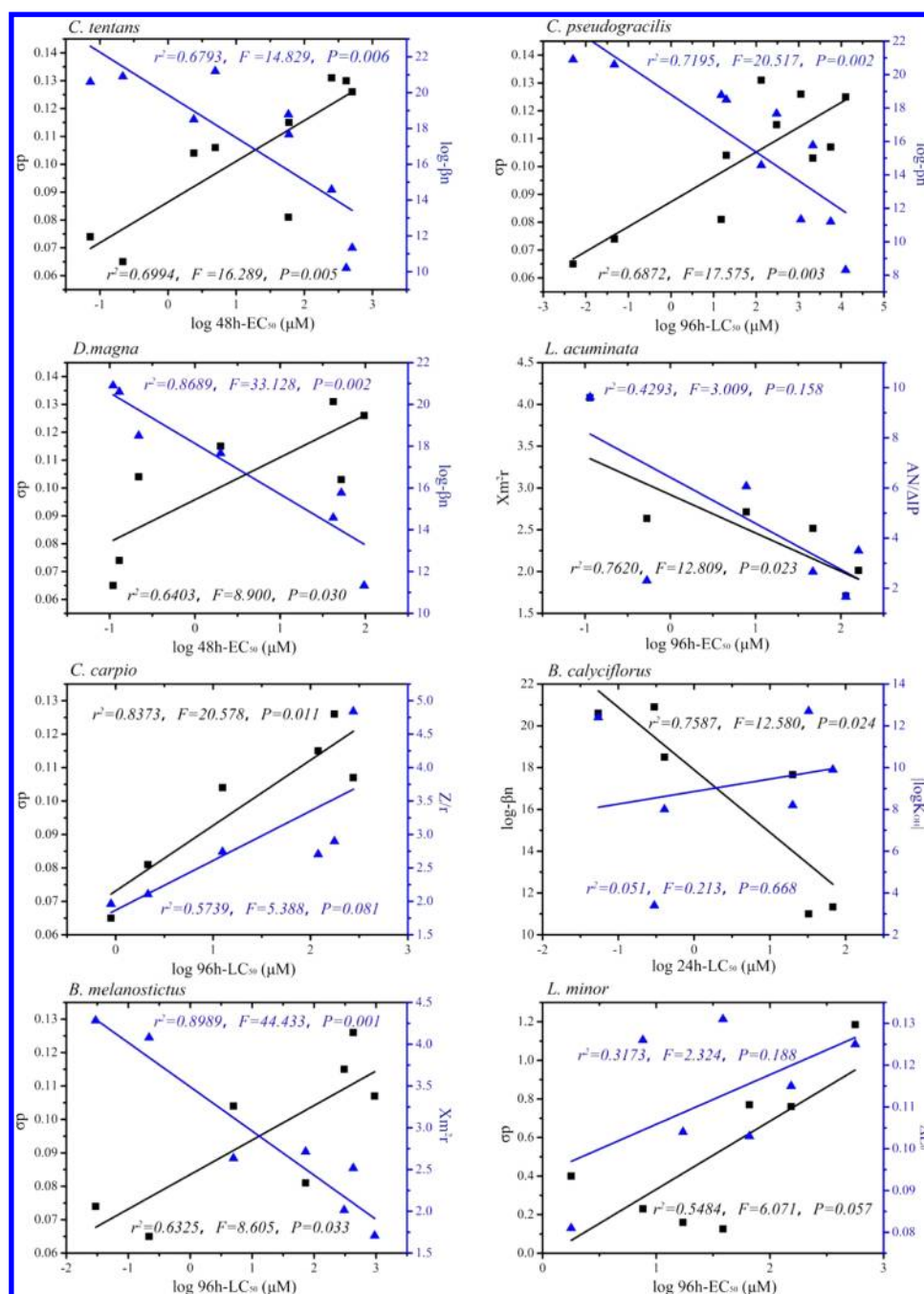
**Figure 1.** Regression models of log $-EC_{50}$ or log $-LC_{50}$ and two most predictive characteristics of ions for eight model organisms.

considered included the assessment end points of survival and growth. (4) Results of acute tests conducted in unusual dilution water, for example, dilution water in which total organic carbon or particulate matter exceeded 5 mg/L, should not be used. All toxicity data of different species were from the ECOTOX Database and literatures.[36−43] In the present study, five phyla and eight different taxonomic families (three chordates, two arthropods, a rotifer, a mollusk and an aquatic plant) were selected (Table 1). Twenty-five metals or metalloids (e.g., mono-, di-, trivalent- and hexavalent metals) were chosen. Those included 16 metals recommended by U.S. EPA in the latest WQC guideline, in which 10 metals had their own CMCs for protecting aquatic life.

**Characteristics of Metals and Development of Predictive Relationships.** Characteristics of the metals used

as parameters in predictive relationships models were obtained from a variety of sources. The basic characteristics considered in developing the relationships were atomic number (AN), atomic radius (AR), Pauling ionic radius ($r$), ionic charge ($Z$), and ionization potential ($\Delta$IP).[44] In total, 14 parameters were considered to characterize the metals in the QICAR model. These parameters included: softness index ($\sigma p$);[45] maximum complex stability constants (log $-\beta_n$), which was derived from maximum strength of complexes formed between metals and EDTA, CN⁻, or SCN⁻; electrochemical potential ($\Delta E_0$);[19] first hydrolysis constants (|log $K_{OH}$|);[46] electronegativity ($Xm$);[47] electron density (AR/AW);[47] relative softness ($Z/rx$), where $x$ represents electronegativity values; atomic ionization potential (AN/$\Delta$IP); covalent index ($X_m^2 r$); polarization force parameters ($Z/r$, $Z/r^2$, and $Z^2/r$); and similar polarization force

parameters ($Z/AR$ and $Z/AR^2$). For each species, measures of acute toxicity were correlated to every characteristic of ions by use of linear regression. The magnitude of association of each characteristic with toxicity was tested by $F$-test statistic, with the level of significance at $\alpha = 0.05$. Because the two-variable model provided better fits and contained sufficient information on structure, the two most predictive characteristics were selected based on the rank of adjusted correlation coefficients,. As a result, multiple linear regressions were performed between the logarithm of $LC_{50}$ or $EC_{50}$ and the two most highly correlated characteristics of ions in Table S1, Supporting Information (SI). The predictive potentials of QICAR models were evaluated by use of the coefficient of determination ($r^2$), residual sum of squares (RSS), root-mean-square deviation (RMSE), $F$ value using multiple analysis of variance (ANOVA), and the level of Type I error ($P$).

**SSD Construction and $HC_5$ Derivation.** On the basis of the QICAR equations developed for each of the representative organisms, predicted acute toxicity values were derived for each metal. After ranking these data from least to greatest, plotting positions (proportions) for use in a cumulative probability distribution were calculated (eq 1).

$$\text{proportion} = (\text{rank} - 0.5)/\text{number of species} \quad (1)$$

To obtain the logarithm of $HC_5$ values, the SSD was fitted by use of the sigmoidal-logistic model (eq 2), where $a$ was represented as an amplitude, $Xc$ was a center value, and $k$ was a coefficient. The CMCs were defined as ($HC_5$)/2. Multiple linear regression and SSD fitting were performed by use of the OriginPro 8 software package, with three fitting parameters ($a$, $Xc$, and $k$) and their standard errors ($a$-SE, $Xc$-SE, and $k$-SE). Significant differences among species were examined by use of ANOVA.

$$y = \frac{a}{1 + e^{-k(x - x_c)}} \quad (2)$$

## ■ RESULTS AND DISCUSSION

**Quantitative Ion Character−Activity Relationships (QICARs) to Predict Toxicity of Metals.** Statistically significant, positive or negative relationships between log $-EC_{50}$ or log $-LC_{50}$ and the 14 ion characteristics were observed. Characteristics with the greatest $r^2$ values for each organism were obtained. Seven characteristics, $\sigma p$, log $-\beta_n$, $X_m^2 r$, AN/$\Delta$IP, $Z/r$, $|\log K_{OH}|$, and $\Delta E_0$ exhibited statistically significant associations with toxicities to representative organisms (Figure 1). The two parameters with the greatest $r^2$ were used to predict the toxicity of each metal for each representative species. The parameter $\sigma p$ was significantly and positively correlated with log $-EC_{50}$ of three arthropods (*C. tentans*, *C. pseudogracilis*, and *D. magna*), with coefficients of determination ($r^2$) of 0.6994 ($F = 16.289$, $P = 0.005$), 0.6872 ($F = 17.575$, $P = 0.003$), and 0.6403 ($F = 8.900$, $P = 0.03$), respectively (Figure 1a, b, and c). These results are consistent with those reported previously where $\sigma p$ was the characteristic that exhibited the strongest association with metal−ligand quantifying binding constant of seven metals for *D. magna*.[28] Log $-\beta_n$ was strongly correlated with acute toxicities of arthropods. Values of log $-\beta_n$ were derived from maximum strength of complexes formed between each metal and EDTA, $CN^-$, or $SCN^-$, which is a measure of binding affinity of each with the O-donor group. The two characteristics that were most predictive of toxicity of metals to mollusks (*L. acuminata*)

were $X_m^2 r$ ($r^2 = 0.7620$, $F = 12.809$, $P = 0.023$) and AN/$\Delta$IP ($r^2 = 0.4293$, $F = 3.009$, $P = 0.158$). Values of $X_m^2 r$ were significantly and negatively correlated with potency of metals. However, the AN/$\Delta$IP ratio was not significantly correlated with toxicity of metals. $X_m^2 r$, which qualifies covalent interactions relative to ionic interactions, is an index of stability of metal ions in water.[48] Absorption of cadmium ions in mussels has been reported to involve covalent interactions with sulfhydryl groups on proteins [49] and that parameter has been used to successfully predict bioaccumulation of metals. This observation suggests that $X_m^2 r$ was a characteristic that was useful for predicting the potency of metals to cause toxicity in mollusks.[48,50] For two organisms of the chordate, *C. carpio* and *B. melanostictus*, $\sigma p$ was correlated with the potency of metals with $r^2 = 0.8373$ ($F = 20.578$, $P = 0.011$) and 0.6325 ($F = 8.605$, $P = 0.033$), respectively. Although the $Z/r$ ratio also provided adequate fits, it was not statistically significant ($r^2 = 0.5739$, $F = 5.388$, $P = 0.081$). Therefore, $\sigma p$ was the only characteristic that was used to predict the potency of metals to cause toxicity to fish. For *B. calyciflorus*, only log $-\beta_n$ was significantly associated with log-$LC_{50}$ ($r^2 = 0.7587$, $F = 12.580$, $P = 0.024$), while $|\log K_{OH}|$ was not significantly correlated ($r^2 = 0.051$, $F = 0.213$, $P = 0.668$). This is consistent with the findings of other researchers, who found that $|\log K_{OH}|$ was not a unique characteristic for predicting the potency of toxicity of metals to rotifer.[27] The two-variable model that best predicted potency of metals was a combination of $\sigma p$ and $\Delta E_0$. The predictive relationships for these two parameters were significant and positive with $r^2 = 0.5484$ ($F = 6.071$, $P = 0.057$) and 0.3173 ($F = 2.324$, $P = 0.188$), respectively. In conclusion, four characteristics of ions, $\sigma p$, log $-\beta_n$, $X_m^2 r$, and $\Delta E_0$, were statistically significantly associated with potencies of metals to the reference species studied here. All these characteristics of ions except for log $-\beta_n$ had been previously reported to be useful in developing QICAR models to predict toxicity of metals. The other three characteristics ($Z/r$, $|\log K_{OH}|$, and AN/$\Delta$IP) could be used as additional factors to improve the predictability.

Eight two-variable linear regression models were developed (Table 1). Among three arthropods, the model for *D. magna* had the best relationships ($r^2 = 0.869$, $F = 13.25$, $P = 0.017$), while the model for *C. tentans* exhibited the poorest coefficient of determination ($r^2 = 0.769$, $F = 9.98$, $P = 0.012$). The QICAR models for *L. acuminata*, *B. calyciflorus*, and *L. minor* had coefficients of determination, which were 0.827, 0.823, and 0.824, respectively. Chordates, compared to other species in the present study, exhibited the best regressions. RSS and MSE were used to evaluate indicators to assess the robustness of the predictive relationships. Because of the diversity of training sets with the maximum number of metal ions ($n = 10$) and valence types (+1 to +3), RSS and MSE were greater for *C. pseudogracilis*, than for other species. On the basis of the results of the multiple regression analysis of variance these characteristics of ions exhibited a statistically significant relationship to log $-EC_{50}$ ($P < 0.05$). Alternatively, equations to predict potency of toxicity of metals to both *L. acuminata* and *B. calyciflorus* were better ($0.05 < P < 0.1$), which were accepted for statistical significance at the 90% confidence level. The QICAR models presented herein were an improvement on the contributions reviewed by Wolterbeek and Walker et al.[29,47] First, the present study further extended the application to 25 metals or metalloids with various valences. Second, more than 20 physicochemical parameters reviewed by Walker et al. and

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their potential to produce toxic effects were examined[29] and then acute toxicities of five phyla and eight species were predicted, including a wide range of aquatic life with different trophic levels. Finally, the two-variable QICAR models for different species were established with indication of which ion characteristic was the most relevant for each species. Base on the analyses of QICAR models for eight species, two-variable correlations appear to be species-specific and also provide major and minor ion characteristics for each species. The presented results demonstrated that all the QICAR models presented herein were capable of predicting potencies of toxicity of metals (RSS < 8.520, MSE < 1.103) that could be used in development of CMCs for these metals.

**Species Sensitivity to Metals and HC$_5$ Derivation.** The predicted acute toxicities of each species were calculated based on eight two-variable linear regression models using seven ion characteristics (see Table S1, SI). Potencies of 25 metals or metalloids to each species, which were derived from QICAR models, varied among species (see Table S2, SI). Planktonic arthropods were most sensitive to Al, As, Fe, Hg, La, Ni, and Pb, with log −EC$_{50}$ values ranging from −1.252 to 1.487. Arthropods were more sensitive to trivalent ions (Al, As, and Fe) in contrast to group IVA, IIB, IIIB and VIII metals. In the present study, it was demonstrated that *C. pseudogracilis* was the most sensitive species to Hg, which agrees with the report of Zhang.[51] However, *B.calyciflorus* was among the most sensitive species to the effects of metals in groups IA, IIA, VIIB and IIB, including Ba, Be, Ca, Cd, K, Li, Mg, Mn, Sr, and Zn, with log −EC$_{50}$ values ranging from −2.225 to 0.751.

*C. pseudogracilis* instead of *D. magna* was the most sensitive to the effects of Cd, a result that is in compliance with the findings that *D. magna* was not the most sensitive species to Cd.[52] For Zn, *C. pseudogracilis* and *D. magna* were equally sensitive with similar log −EC$_{50}$ values of 0.594 and 0.669. This finding also agrees with reports that proposed that freshwater crustaceans were the most sensitive to Zn.[53] In conclusion, zooplankton were most vulnerable to the toxic effects of metals, which is also consistent with previous conclusions based on empirical measures of toxic potency.[54−56] Among the three arthropods, *C. tentans*, *C. pseudogracilis*, and *D. magna*, *D. magna* was the most sensitive species to major metals. This conclusion corresponds to the results of Song et al.,[57,58] who found that *D. magna* was more sensitive to triphenyltin than *C. tentans*, with 24 h-LC$_{50}$ values of 13.3 and 287.7 μg/L. The mollusk, *L. acuminate*, was the most sensitive organism to Ag, Co, Cu, Sb, and Tl, which are group IIIA, VA, VIII, and IB metals. This was also in compliance with the results of a previous study.[59] Compared to other organisms, the vertebrates, *C. carpio* and *B. melanostictus*, were the least sensitive to metals except Na. *L. minor* was the representative of aquatic plants, since metals affected its microstructures and cell growth. *L. minor* was among the most sensitive organisms to Cr(III) and Cr(VI) (see Table S2, SI), which was consistent with previous studies in which exposure to Cr resulted in lesser production of biomass of *L. minor*.[60] In conclusion, five phyla and eight families of representative organisms were used as minimum set of species to establish models of sensitivity to metals. In accordance with requirements of the U.S. EPA, all of the species were found to be sensitive to the toxic effects of main group metals (IA−VA) and metals in groups IIB, IIIB, VIIB, and VIII.

Species sensitivity distributions for 25 metals or metalloids were constructed and ultimately used to predict CMCs. The basic fitting parameters (a, Xc, k, a-SE, Xc-SE, and k-SE) and

statistical indexes (Adj.r$^2$, RSS, F and P) used to develop the predictive relationships are shown in Table S3, SI. Coefficients of determination (r$^2$) of the 25 fitting equations were greater than 0.9 (RSS < 0.0437, P < 0.0001), which suggests that all SSD models provided adequate fits to the data. However, the predicted toxicities for every species in the Al-SSD model were similar, which was insufficient to provide a reasonable fit. The SSD for Al that contains more sensitive species needs to be further investigated.

**Distributions of 25 Metal Criteria and Correlation Analyses.** On the basis of the SSD curves of 25 metals or metalloids in Figure 2, the toxicity profiles were classified as
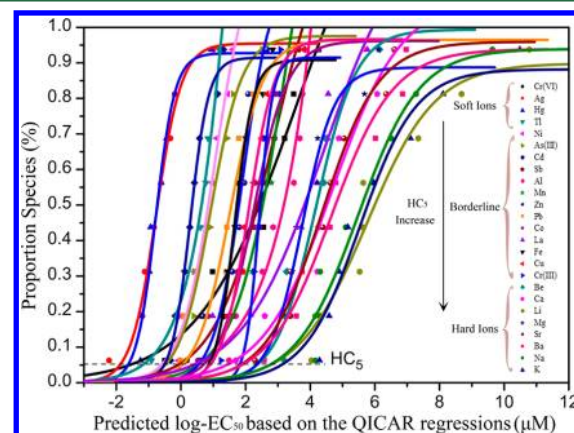


**Figure 2.** Species sensitivity distributions analysis and derivation of the predicted log −HC$_5$ based on the QICAR regressions for 25 metals or metalloids. The predicted toxicities were derived from minimum eight species (three phyla), including *C. tentans*, *C. pseudogracilis*, *D. magna*, *L. acuminata*, *C. carpio*, *B. calyciflorus*, *B. melanostictus*, and *L. minor*.

highly toxic, moderately toxic, low toxic and lesser toxic within the whole concentration thresholds between −1.89 and 3.11. Cr (VI), Ag, Hg, and Tl were classified as highly toxic metals, with log −HC$_5$ values between −1.89 and −1.0. As (III), Cd, Cu, and Sb were classified as moderately toxic metals, with log −HC$_5$ values ranging from −1.0 to 0. Al, Co, Fe, La, Mn, Ni, Pb, and Zn were classified as low toxic metals with log −HC$_5$ values from 0 to 1.0. The rest of the metals caused lesser acute toxicity at the concentrations tested, with log −HC$_5$ values from 1.0 and 3.11.

Correlations between log −HC$_5$ and seven characteristics of metal ions were good indicators for prediction of the toxicity of free ions. The coefficient of determination ranked in the descending order was $\sigma p > \log -\beta_n > \Delta E_0 > X_m^2 r > |\log K_{OH}| > Z/r > AN/\Delta IP$ (See Table S4, SI). In the present study, $\sigma p$ and log −$\beta_n$ were significantly correlated with log-HC$_5$, with adjusted correlation coefficients of 0.7638 (F = 78.626, P = 7.02 × 10$^{-9}$) and 0.7265 (F = 64.760, P = 3.88 × 10$^{-8}$), respectively. The relationships of actual and model predicted log −HC$_5$ with softness index ($\sigma p$) were shown in Figure 3. The softness index $\sigma p$ separated metal ions into three groups based on their solubility constants with sulfur and oxygen-containing anions: (1) hard ions, which preferentially bind to oxygen or nitrogen (e.g., Li, Na, Ca, and Mg); (2) soft ions, which preferentially bind to sulfur (e.g., Cd, Hg, Ag, and As(III)); and (3) borderline ions, which form complexes with oxygen, nitrogen, and sulfur to varying degrees (e.g., Co, Ni, Cu, and Zn). Most soft ions were classified as having high and intermediate toxic potency ($\sigma p$ < 0.10); borderline ions were
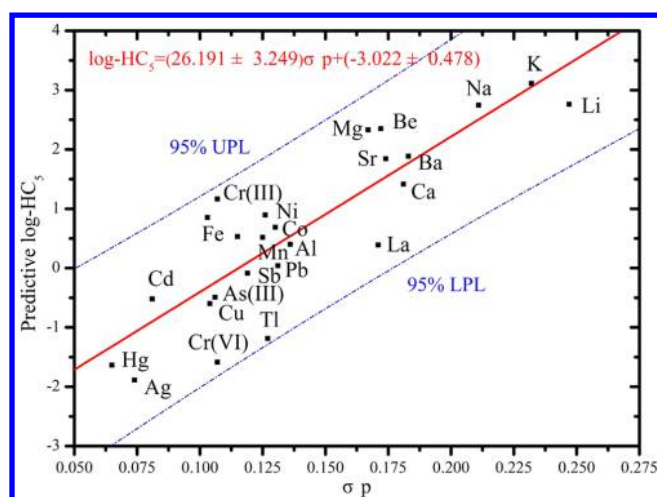
**Figure 3.** Model for log $-HC_5$ and softness index ($\sigma$p) at 95% prediction level.

less toxic ($0.10 < \sigma p < 0.163$); and hard ions exhibited lesser potency ($0.163 < \sigma p < 0.250$). These findings support the conclusion that $\sigma$p is the best predictor of toxic potency of metals or metalloids to aquatic organisms. Alternatively, log $-\beta_n$ had the greatest negative correlation with toxicity, which reflected the binding affinities of metal−ligand complexes. Values of log $-\beta_n$ of more toxic metals, such as Hg, Ag, and Tl, were greater than 18.0, while those for metals of intermediate toxicity were between 11.0 and 18.0. Both $\Delta E_0$ and $X_m^2 r$ were weakly correlated ($P < 0.001$) and the rest of the descriptive parameters were not significantly ($P > 0.05$) correlated with toxic potency. Thus, the minimum set of characteristics of metal ions required to reasonably predict WQC of 25 metals were $\sigma$p, log $-\beta_n$, $\Delta E_0$, $X_m^2 r$, |log $K_{OH}$|, $Z/r$, and AN/$\Delta$IP, while not strongly predictive, can be used as complementary parameters to discriminate among potencies of metals to aquatic organisms.

**Validation and Applicability of the QICAR-SSD Model.** Values of log $-HC_5$ for 10 metals derived from CMCs recommended by U.S. EPA in 2009 are shown in Figure 4. The QICAR-SSD model herein demonstrated a good performance to predict log-$HC_5$. The order of standard errors between predicted values and values recommended by U.S. EPA were
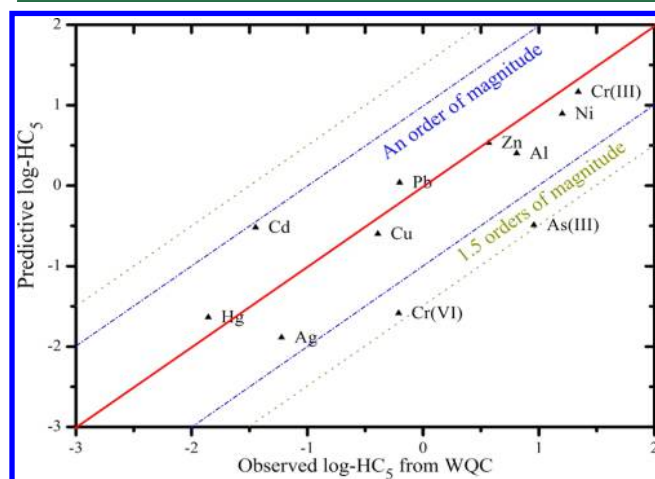


**Figure 4.** Relationships between predicted log $-HC_5$ and recommended log $-HC_5$ derived from WQC.

Zn < Cr (III) < Cu < Hg < Pb < Ni < Ag < Cd < Al < Cr (VI) < As (III). The predicted CMC for Zn was 120 $\mu$g/L and the CMC recommended by the U.S. EPA was 110.9 $\mu$g/L. The model provided the poorest prediction of the potency of As (III). The predicted CMC was 12.16 $\mu$g/L, and the CMC value by U.S. EPA was 340 $\mu$g/L. In summary, the comparison results indicate that values of log −CMCs predicted by this study and log −CMCs recommended by U.S. EPA for Zn, Cr (III), Cu, and Hg were in the same order of magnitude. The differences of values for Pb, Ni, Ag, and Cd were within 1 order of magnitude, and for the rest metals or metalloids, the differences were within 1.5 orders of magnitude. Of these metals, the CMCs recommended by U.S. EPA for Hg, Cu, Cr (III), Zn, Ni, and Pb were well reproduced by the models with differences of less than 0.20-fold. The model provided reasonable predictions for Ag and Cd with standard error between 0.20 and 1.00. For Ag, the toxicity prediction equation for the sensitive species *L. acuminata* contains two sensitive characteristics of metal ions, $X_m^2 r$ and AN/$\Delta$IP, which resulted in greater toxicity prediction error and SSD fitting errors. For Cd, it water hardness can influence aquatic toxicity. When acute toxicity of Cd to *D. magna* was determined at three different harnesses, it was found that the toxicity in softer water was 5 times greater than that harder water.[4] However, the QICAR-SSD model only focuses on the influence of physicochemical properties of metals and neglects site-specific geochemical conditions such as hardness, pH, temperature, dissolved oxygen, and dissolved organic matter. Indeed, site-specific geochemical conditions influence the degree to which organisms take up metals and exhibit adverse effects. It is critical to consider bioavailability in extended QICAR-SSD model, as geographically distinct eco-regions and sites will show distinctive geochemical character-istics.

Trivalent and hexavalent metals (Al (III), As (III), and Cr (VI)) provided weak prediction because of the average deviation of 1.4 orders of magnitude. Of the seven character-istics of metal ions, $\sigma$p exhibited the greatest statistical significance to predict log-$HC_5$, with the linear regression slope of 26.408 ($F = 78.626$, $P = 7.02 \times 10^{-9}$). Therefore, $\sigma$p of more charged metals need to be revised by increasing the value by a factor of 0.05 ($1.387/26.408$). However, valences of metal ions affected the magnitude of $\sigma$p, which is the reason that the ratio of coordinate bond energy of iodide to coordinate bond energy of fluoride will increase after highly charged metals combine covalently to bioligands.[47] In QICAR-SSD model, the $\sigma$p per unit charge was used as a criterion for evaluation with the cumulative contribution of charge neglected. In further investigation, the QICAR-SSD model for highly charged metals should be developed to raise accuracy of predicted WQCs.

To provide reasonable predictions of the toxicity of metals to various organisms, one needs to consider many factors since each metal has unique physicochemical property that will make differences in its environmental behavior and toxic mechanism to sensitive species. How to predict toxicity of metals to all species under various conditions from limited information is the key issue to the WQC study. Although the models presented can reasonably predict toxicity of metals from limited information, they do need to be further developed in five areas. These include (1) QICAR models for additional representative species in order to expend the protection range of WQC; (2) modeling metal toxicity separately by metal valence might improve the prediction accuracy of the model; (3) the need to account the effect of site-specific geochemical conditions, such

as hardness, pH, temperature, dissolved oxygen and dissolved organic matter; (4) optimization can be further generalized throughout the entire predictive framework; and (5) bioavailability of multiple metal speciation due to transformation should also be considered. These predictive models could be useful when data on metal toxicity are lacking or incomplete. While further development of such models is necessary to determine their range of applicability, the QICAR-SSD model is a promising screen level tool that can be used to rapidly predict aquatic toxicity and criteria of metals.

## ■ ASSOCIATED CONTENT

### ⓢ Supporting Information

Tables with seven metal ion characteristics used in regression models, predicted log $-EC_{50}$ values of minimum eight species, SSD fitting parameters and correlations between metal ion characteristics, and predicted log $-HC_5$. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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