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Using Metal-Ligand Binding Characteristics to Predict Metal Toxicity: Quantitative Ion Character–Activity Relationships (QICARs)

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Ecological risk assessment can be enhanced with predictive models for metal toxicity. Modelings of published data were done under the simplifying assumption that intermetal trends in toxicity reflect relative metal–ligand complex stabilities. This idea has been invoked successfully since 1904 but has yet to be applied widely in quantitative ecotoxicology. Intermetal trends in toxicity were successfully modeled with ion characteristics reflecting metal binding to ligands for a wide range of effects. Most models were useful for predictive purposes based on an F-Ratio criterion and cross-validation, but anomalous predictions did occur if speciation was ignored. In general, models for metals with the same valence (i.e., divalent metals) were better than those combining mono-, di-, and trivalent metals. The softness parameter (σw) and the absolute value of the log of the first stability constant (log K1) were especially useful in model construction. Also, ΔE, contributed substantially to several of the two-variable models. In contrast, quantitative attempts to predict metal interactions in binary mixtures based on metal–ligand complex stabilities were not successful. — Environ Health Perspect 106(Suppl 6):1419-1425 (1998).


Key words: metal, toxicity, prediction, model, ion characteristics

Quantitative structure–activity relationships (QSARs) are applied widely to predict bioactivity (e.g., toxicity or bioavailability) of organic compounds. In contrast, models relating metal ion characteristics to their bioactivity remain underexploited. A few models exist for human risk prediction [e.g., Williams et al. (1)] but quantitative models have not been fully explored for nonhuman species. This is surprising because such quantitative ion character–activity relationships (QICARs) would be extremely useful for predicting effects of untested metals during risk assessment activities. Also, qualitative ion character–activity relationships (ICARs) based on simple metal–ligand binding have been described in the literature for nearly a century. As an example, Mathews (20) assumed that metals were most active in their ionic form (the ionic hypothesis) and correlated metal toxicity to characteristics of ion binding to biomolecules. Especially useful were characteristics reflecting bond stability with ligand groups possessing O, N, and S donor atoms. For the last half-century, permutations on this approach were applied successfully by Jones (3, 4), Binet (5), Loeb (6), McGuigan (7), Biesinger and Christensen (8), Jones and Vaughn (9), Kaiser (10), Williams and Turner (11), Babich et al. (12, 13), Fisher (14), Newman and McCloskey (15), McCloskey et al. (16), and Tatara et al. (17, 18). Modeling was often based on hard and soft acid and base theory (9, 11, 19).

This approach has not been evaluated for its predictive usefulness despite clear indications from ICARs that QICARs were feasible. Newman and McCloskey (15) suggested that the contrasting extent of QSAR and QICAR development resulted from two factors. First, the QSAR approach was quickly incorporated into ecotoxicology because it had already proven its worth in pharmacology and human toxicology. In contrast, QICARs were not well established in pharmacology or human toxicology because the major focus of these disciplines was organic drugs and poisons. Second, chemical speciation complicates prediction because several metal species are present simultaneously and the bioavailability of each is ambiguous. However, some of this ambiguity can be removed by judiciously applying the free ion activity model (FIAM) (20). The FIAM, an extension of the ionic hypothesis, holds that the bioactivity of a dissolved metal is correlated with its free ion concentration or activity. The complication of simultaneous exposure to many species can be minimized by focusing on the free ion. Because both impediments are resolvable, no inherent obstacle impedes QICAR development to the same level of utility as that of QSARs.

This paper assesses the QICAR approach for predicting metal toxicity. This is done by reanalyzing metal effects data reported elsewhere. Models are assessed by cross-validation (PRESS method as described in "Methods") relative to their effectiveness for predicting bioactivity of untested metals. An attempt is also made to extend this approach to prediction of metal interactions in binary mixtures.

Methods

Data Sets

Nineteen published data sets were selected that report effects for an adequate number and range of metals (Table 1). To reinforce the generality of conclusions, we used data for widely differing species, metals, modes of exposure, and effects. To avoid bias in conclusions, only the most comprehensive data set was selected if very similar sets existed. Published data sets involved...
enzyme inactivation (21,22), viability of cultured metazoan cells including cells from two fish (12,23) and a mammal (24), germination inhibition of two fungi (25), bioaccumulation in a marine diatom (14), inhibition of bacterial bioluminescence (Microtox assay, Microbics Corporation, Carlsbad, California) (16), and acute toxicity to soil nematodes (17,18). Acute toxicity was also examined for diverse aquatic invertebrates including a planarian (4), cladoceran (26), insect (1), and amphipod (27). Several data sets involved chronic exposures with lethal (1,3,8) or sublethal (8) end points. For all studies, barium toxicity was excluded from models because of its very specific interference with K+ flux in excitable tissues of metazoans (28–31).

### Ion Characteristics

One- and two-explanatory variable models were constructed from six ion qualities. The electronegativity ($\chi_m$) and Pauling ionic radius ($r$) were combined to produce a covalent index ($\chi_m^2 r$) reflecting the relative importance of covalent versus electrostatic interactions during metal–ligand binding (32). The ion charge ($Z$) and Pauling ionic radius were combined to generate a second index, the cation polarizing power ($Z^2 r$), reflecting the energy of the metal ion during electrostatic interaction with a ligand (32). However, no models using $Z^2 r$ were reported here because this index did not contribute to the best candidate model for any data set. A softness index ($\sigma_2$) (9,11) was produced by dividing the difference between the coordinate bond energies of the metal fluoride and iodide by the coordinate bond energy of the metal fluoride. This index reflected metal ion softness, the relative tendency for the outer electron shell to deform (polarizability), and the ion's tendency to share electrons with ligands. Metal affinity to intermediate ligands such as those with O donor atoms was estimated with another index ($\log K_{OH}$) based on the first hydrolysis constant of the ion, i.e., $K_{OH}$ for $M^{n+} + H_2O \rightarrow MOH^{n-} + H^+$ (15). Following the approach of Kaiser (10), AN/DIP and $\Delta E_4$ were also explored in model development. Log AN/DIP did not improve models, as suggested by Kaiser (10); AN/DIP was used instead. Atomic number (AN), notionally reflecting ion inertia or size, was combined with DIP (the difference in ionization potentials for the ion oxidation number OX and OX-1), which reflected ionization potential. The absolute difference between the electrochemical potential of the ion and its first stable reduced state ($\Delta E_4$) reflected an ion's ability to change electronic state. Values for these ion characteristics used in this study are tabulated by McCluskey et al. (16).

### Model Assessment

Linear regression models were generated with these six variables ($\chi_m^2 r$, $Z^2 r$, $\sigma_2$, $\log K_{OH}$, $\Delta E_4$).
PREDICTING METAL TOXICITY

High correlation coefficients were associated with many one- and two-variable models for divalent metal effects (Figure 1 and Table 2). Based on a stringent criterion of an $F$ ratio $\geq 5$, 13 of the 19 data sets had at least one model of predictive utility. Data sets failing to produce useful models involved cultured cell viability (three studies), in vivo inactivation of carbonic anhydrase, and inhibition of fungal germination. Fruit fly mortality data also failed to produce a useful model according to our stringent criterion but nevertheless had a high $F$ ratio of 4.5. One- or two-variable models of most predictive promise included $\log K_{OH}$ or $\sigma_p$. Several two-variable models, especially those including $\Delta E_{\text{p}}$ were also among those with predictive promise. The covalent index ($\chi^2_{\text{C}}$) alone or combined with another variable never produced the best model for any data set. Five of the thirteen most informative models (MAICE) were single-variable models. The median $r^2$ for these best and predictively useful models was 0.90 (range 0.78 to 0.97). Approximately 90% of the variation in metal effect could be explained by the models.

Results

Models for Divalent Metals

Bacterial bioluminescence data for binary mixtures of metals (15) were examined statistically to assess the hypothesis that metals with strong and similar covalent binding to ligands will interact strongly. The qualitative conclusions of Newman and McCloskey (15) were tested statistically for two series of mixtures: Cu in combination with Ca, Cd, Hg, Mg, Mn, Ni, Pb, or Zn; and Mg in combination with Ca, Cd, Hg, Mn, Ni, Pb, or Zn. Interactions were assessed statistically using the SAS Procedure MIXTURE (33) with an interaction term (i.e., metal$_1 \times$metal$_2$). Statistical significance and magnitude of the interaction terms were used to assess interactions between paired metals. If the above hypothesis was correct, the intensity of interaction would be greatest between Cu and similar metals (e.g., Hg or Cd) and lowest for Cu and dissimilar metals (e.g., Mg or Ca). In the second series of mixtures there would be little interaction between Mg and other metals.

**Figure 1.** Representative data illustrating the relationship between metal effects and metal ion characteristics. Responses range widely from enzyme inhibition (lactic dehydrogenase, LDH) (22) to toxicity of cultured turbot cells (23) to acute lethality of a crustacean (amphipod) (27) to chronic toxicity of mice (1) and *Daphnia magna* (8).
Cross-validation of the best divalent metal models (Table 3) indicated that the median deviations between observed and predicted effects were small. The median deviations were less than 22%; most were closer to 10%. For comparison, a well-known QSAR model for bioconcentration of eight organic compounds in fish (37) had a median difference of ~7% and an interquartile range of −13 to 14%. However, many models poorly predicted effects for specific metals. These metals tended to be extreme class a (e.g., Mg), class b metals that undergo considerable speciation in solution (e.g., Hg, Pb), or metals with the tendency to precipitate from solution (e.g., Mn). Under the assumption that speciation contributed to some of these poor predictions by models built from total metal concentrations, concentrations of free metal ion were estimated with the MINTEQA2 Version 3.10 program (38) for two data sets involving bacterial bioluminescence (15, 16). These assays were conducted in contrasting media having speciation similar to marine (15) or freshwater (16) environments. Except for Hg in media having speciation similar to marine systems, EC50 values of metals were expressed as the free ion concentration. The EC50 for Hg was expressed in terms of the free ion plus neutral chloro complex concentration because neutral chloro complexes of Hg can also be bioavailable (39). In both media the extremely discordant predictions were greatly diminished or eliminated if EC50 values were expressed in terms of the speciated metal concentration (Table 3).

**Models Including All Metals**

Although correlation coefficients were lower than those for the divalent metal models (median 0.80, range 0.67 to 0.87), useful models including all metals (mono-, di-, and trivalent) were generated for 13 of the 19 data sets (Table 4). Approximately 80% of the variation in effect for metals could be attributed to the explanatory variables. Eight of thirteen data sets producing useful models had the best (MAICE) model involving only one explanatory variable. Again, the llog Kow or Sp indices contributed to many of the best one-variable models. As with the divalent metal models, data sets failing to produce useful models tended to be those for in vivo enzyme inactivation or cultured cell viability. Data for bioaccumulation of metals in a marine diatom and crustacean toxicity also failed to produce useful models.

**Metal Mixtures**

Although there were qualitative indications of concentration-dependent interactions between metals with similar and high cova- lent binding tendencies, no such trends were noted in this formal analysis. The only significant trends in the intensity of the interaction term for both series of mixtures was a consequence of increasing LC50 values with decreasing covalent interactions; this trend was an artifact of the data structure. Regardless of whether Cu or Mg was combined with metals, there was a upward trend in the interaction term, with increasing tendency of the competing metal to interact covalently with ligands. Such a trend for the Mg series of binary mixtures was inconsistent with predictions from the initial hypothesis. The results did not support the
initial hypothesis that mixture interactions could be predicted from the tendency to covalently bind with ligands.

Conclusion

Quantitative ion character—activity relationships can be developed for a range of effects based on metal–ligand binding theory. Estimations of speciation and application of the FIAM were not required to develop useful QICARs for some metals in the data sets. Our work with QICAR development for microbial bioluminescence (15,16) and nematode toxicity (17,18) supports this observation. However, there are clear indications that calculation of free ion concentrations or activities will greatly improve modeling, i.e., eliminate or reduce the magnitude of anomalous predictions for some class b metals.

The results for the relatively simple in vitro enzyme inactivation and cultured cell viability studies illustrate the difficulties associated with using models based on total metal concentration. These data sets involved buffered or complex media, i.e., the enzyme inactivation in a buffered phosphate solution and cell culture experiments in complex media containing components such as 10% fetal calf serum. Another data set failing to produce a useful model was associated with a high ionic strength media, i.e., bioaccumulation in a marine diatom.

Table 3. Cross-validation of the best models for divalent metals.  

<table>
<thead>
<tr>
<th>Data set</th>
<th>Median, %</th>
<th>Interquartile range (IQR, %)</th>
<th>Extreme predictions, % deviation ≥ 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic dehydrogenase</td>
<td>13</td>
<td>-53 to 21</td>
<td>-1484 (Cu)</td>
</tr>
<tr>
<td>Glutamic oxalacetic transaminase</td>
<td>4</td>
<td>-15 to 27</td>
<td>-9806 (Hg)</td>
</tr>
<tr>
<td>Bacteria, freshwater (V. fischeri)</td>
<td>-9</td>
<td>-445 to 13</td>
<td>-1510 (Pb)</td>
</tr>
<tr>
<td>Bacteria, freshwater (V. fischeri) specified</td>
<td>6</td>
<td>-17 to 22</td>
<td>-445 (Cu)</td>
</tr>
<tr>
<td>Bacteria, marine (V. fischeri)</td>
<td>7</td>
<td>-55 to 15</td>
<td>-1027 (Hg)</td>
</tr>
<tr>
<td>Bacteria, marine (V. fischeri) specified</td>
<td>12</td>
<td>-28 to 52</td>
<td>-149 (Hg)</td>
</tr>
<tr>
<td>Diatom</td>
<td>1</td>
<td>-30 to 13</td>
<td>-325 (Mg)</td>
</tr>
<tr>
<td>Fungi (Botrytis fabae)</td>
<td>21</td>
<td>-47 to 57</td>
<td>135 (Ca)</td>
</tr>
<tr>
<td>Nematode (Caenorhabditis elegans)</td>
<td>12</td>
<td>-24 to 30</td>
<td>182 (Pb)</td>
</tr>
<tr>
<td>Planaria (Polyceis nigra)</td>
<td>-6</td>
<td>-46 to 105</td>
<td>132 (Mn)</td>
</tr>
<tr>
<td>Daphnia magna (48-hr LC50)</td>
<td>-6</td>
<td>-40 to 21</td>
<td>105 (Pb)</td>
</tr>
<tr>
<td>Daphnia magna (reproduction)</td>
<td>22</td>
<td>-154 to 268</td>
<td>250 (Mg)</td>
</tr>
<tr>
<td>Daphnia magna (3-week LC50)</td>
<td>-1</td>
<td>-9 to 7</td>
<td>101 (Mg)</td>
</tr>
<tr>
<td>Amphilopod (Cranogonyx pseudogracilis)</td>
<td>19</td>
<td>-31 to 70</td>
<td>105 (Pb)</td>
</tr>
<tr>
<td>Three-spined stickleback</td>
<td>-7</td>
<td>-83 to 23</td>
<td>100 (Co)</td>
</tr>
<tr>
<td>Mouse</td>
<td>8</td>
<td>-8 to 17</td>
<td>-258 (Mn)</td>
</tr>
</tbody>
</table>

*Deviations are expressed as percentages, [abs (observed effectmetal − predicted effect model without metal) / observed effectmetal]×100.

Table 4. Correlation coefficients (r²) for models with all metals (mono-, di- and trivalent metals).  

<table>
<thead>
<tr>
<th>Study</th>
<th>χ²</th>
<th>σp</th>
<th>log Kd</th>
<th>χ²</th>
<th>AN/ΔIP</th>
<th>ΔE</th>
<th>log Kd</th>
<th>σp</th>
<th>ΔE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase</td>
<td>0.23 N</td>
<td>0.59 S</td>
<td>0.25 N</td>
<td>0.35 N</td>
<td>0.28 N</td>
<td>0.59 N</td>
<td>0.78 S</td>
<td>0.49 S</td>
<td>0.60 N</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>0.79 S</td>
<td>0.49 N</td>
<td>&lt;0.01 N</td>
<td>0.79 S</td>
<td>0.57 N</td>
<td>0.50 N</td>
<td>0.52 N</td>
<td>0.08 N</td>
<td>0.70 N</td>
</tr>
<tr>
<td>Glutamic oxalacetic transaminase</td>
<td>0.84 S</td>
<td>0.60 S</td>
<td>&lt;0.01 N</td>
<td>0.86 S</td>
<td>0.60 N</td>
<td>0.67 N</td>
<td>0.75 S</td>
<td>0.05 N</td>
<td>0.91 N</td>
</tr>
<tr>
<td>Turbot (TF) cells</td>
<td>0.01 N</td>
<td>0.85 S</td>
<td>0.01 N</td>
<td>0.06 N</td>
<td>0.02 N</td>
<td>0.08 N</td>
<td>0.95 S</td>
<td>0.95 S</td>
<td>0.91 N</td>
</tr>
<tr>
<td>Bluegill (BF-2) cells</td>
<td>0.10 N</td>
<td>0.60 S</td>
<td>0.05 N</td>
<td>0.15 N</td>
<td>0.31 N</td>
<td>0.76 N</td>
<td>0.60 N</td>
<td>0.18 N</td>
<td>0.67 N</td>
</tr>
<tr>
<td>Hamster cells</td>
<td>0.55 S</td>
<td>0.75 S</td>
<td>0.11 N</td>
<td>0.55 S</td>
<td>0.62 S</td>
<td>0.83 N</td>
<td>0.86 S</td>
<td>0.67 N</td>
<td>0.86 N</td>
</tr>
<tr>
<td>Bacteria (V. fischeri)</td>
<td>0.70 S</td>
<td>0.80 S</td>
<td>0.49 S</td>
<td>0.84 S</td>
<td>0.88 S</td>
<td>0.84 S</td>
<td>0.75 S</td>
<td>0.75 S</td>
<td>0.75 S</td>
</tr>
<tr>
<td>Diatom</td>
<td>0.44 S</td>
<td>0.60 S</td>
<td>0.44 S</td>
<td>0.68 S</td>
<td>0.73 N</td>
<td>0.73 S</td>
<td>0.73 N</td>
<td>0.73 N</td>
<td>0.73 N</td>
</tr>
<tr>
<td>Fungi (Alternaria tennis)</td>
<td>0.59 S</td>
<td>0.67 S</td>
<td>0.56 S</td>
<td>0.74 S</td>
<td>0.67 N</td>
<td>0.71 S</td>
<td>0.71 N</td>
<td>0.71 N</td>
<td>0.71 N</td>
</tr>
<tr>
<td>Fungi (Botrytis fabae)</td>
<td>0.58 S</td>
<td>0.69 S</td>
<td>0.56 S</td>
<td>0.74 S</td>
<td>0.76 N</td>
<td>0.72 S</td>
<td>0.77 N</td>
<td>0.75 S</td>
<td>0.75 S</td>
</tr>
<tr>
<td>Nematode</td>
<td>0.55 S</td>
<td>0.49 S</td>
<td>0.69 S</td>
<td>0.80 S</td>
<td>0.56 S</td>
<td>0.70 N</td>
<td>0.54 N</td>
<td>0.72 S</td>
<td>0.72 S</td>
</tr>
<tr>
<td>(Caenorhabditis elegans)</td>
<td>0.35 S</td>
<td>0.70 S</td>
<td>0.29 S</td>
<td>0.43 N</td>
<td>0.47 N</td>
<td>0.71 S</td>
<td>0.70 N</td>
<td>0.41 N</td>
<td>0.41 N</td>
</tr>
<tr>
<td>Planaria (Polyceis nigra)</td>
<td>0.52 S</td>
<td>0.80 S</td>
<td>0.58 S</td>
<td>0.66 N</td>
<td>0.67 N</td>
<td>0.82 N</td>
<td>0.80 N</td>
<td>0.66 N</td>
<td>0.66 N</td>
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<tr>
<td>Daphnia magna (48-hr LC50)</td>
<td>0.50 S</td>
<td>0.68 S</td>
<td>0.28 S</td>
<td>0.54 S</td>
<td>0.43 S</td>
<td>0.74 S</td>
<td>0.76 N</td>
<td>0.71 S</td>
<td>0.71 S</td>
</tr>
<tr>
<td>Daphnia magna (reproduction)</td>
<td>0.47 S</td>
<td>0.70 S</td>
<td>0.30 S</td>
<td>0.52 S</td>
<td>0.83 S</td>
<td>0.75 S</td>
<td>0.77 N</td>
<td>0.71 S</td>
<td>0.71 S</td>
</tr>
<tr>
<td>Fruit fly</td>
<td>0.43 S</td>
<td>0.56 S</td>
<td>0.13 N</td>
<td>0.46 N</td>
<td>0.87 S</td>
<td>0.57 S</td>
<td>0.59 N</td>
<td>0.39 N</td>
<td>0.39 N</td>
</tr>
<tr>
<td>(Drosophila melanogaster)</td>
<td>0.27 N</td>
<td>0.68 S</td>
<td>&lt;0.01 N</td>
<td>0.27 N</td>
<td>0.46 S</td>
<td>0.71 N</td>
<td>0.69 S</td>
<td>0.05 N</td>
<td>0.05 N</td>
</tr>
<tr>
<td>Amphipod (Cranogonyx pseudogracilis)</td>
<td>0.63 S</td>
<td>0.71 S</td>
<td>0.42 S</td>
<td>0.71 S</td>
<td>0.76 S</td>
<td>0.71 S</td>
<td>0.74 S</td>
<td>0.63 S</td>
<td>0.63 S</td>
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<tr>
<td>Three-spined stickleback</td>
<td>0.20 N</td>
<td>0.71 S</td>
<td>0.05 N</td>
<td>0.23 N</td>
<td>0.50 N</td>
<td>0.76 S</td>
<td>0.73 S</td>
<td>0.39 S</td>
<td>0.39 S</td>
</tr>
</tbody>
</table>

*Correlation coefficients are bold for models with all significant covariates and an F ratio ≥ 5.0. The specific ions fit to each models are listed in Table 1. Statistical significance is noted by a σp, N for S, N. For the [σp, log Kd] model indicates that σp did not, but [log Kd] did, contribute significantly to the model. *Characteristics(s) providing the best model (MAICE).
This association of model failure with complex exposure media suggests that speciation calculation would improve modeling because speciation is most extensive under these conditions. This is further supported by the diminution of deviations from perfect prediction during cross-validation of models considering speciation. If speciation is ignored, predictions of effect should be done cautiously for class b and some intermediate metals characterized by extensive speciation in solution. Published trends for metal speciation in marine (40) and freshwater (40, 41) systems can be used to identify those metals for which speciation should be considered during QICAR development.

The ion characteristics of most general value in constructing QICARs were log $K_{OH}$ and $\sigma_p$, although other variables such as $\Delta E_p$ were also important in several models. The log $K_{OH}$ reflects the tendency for a metal ion to form a stable complex with intermediate ligands. Intermediate ligands on biomolecules would include groups with O donor atoms (e.g., carboxyl groups). This suggested that binding with such functional groups is important in determining the relative bioactivity of metals. The softness index ($\sigma_p$) quantifies the ability of a metal ion to accept an electron during interaction with a ligand. It reflects the importance of covalent interactions relative to electrostatic interactions (32) in determining intermetal trends in bioactivity.

The results also suggest that QICARs based on the characteristics used in this study are best developed for metals of similar charge. Although models based on variables such as $\sigma_p$ did produce viable models, Ahrlan (42) and Williams and Turner (11) argue against the application of $\sigma_p$ for metals differing in charge. Instead, variables adjusting for differences in charge, such as $\sigma_1$ (11), may be required.

Effective application of the QICAR approach may also be improved by careful examination of the values used to generate the explanatory variables. Considerable judgment is required when selecting among published estimates. More involved analysis of these data for application to QICAR generation is currently required. Regardless, QICARs are now feasible, especially if they were produced with speciation concentrations for metals of similar charge.

Ecological risk assessment would be enhanced by reliable models for predicting effects of untested metals from known effects of tested metals. In the absence of complete information on the effect of all metals of concern on each important species under a variety of conditions, the ability to interpolate from existing data to predict effects for untested metals would improve the accuracy of assessments. QICARs would be particularly useful in preliminary screening and in situations analogous to those in which QSARs are currently applied. Our results suggest that the QICAR approach would be extremely useful for this purpose. However, several resolvable issues require attention before the QICAR approach has the same general usefulness as the QSAR approach. These issues include exploration of more explanatory variables, careful evaluation of ionic qualities used to calculate explanatory variables, examination 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 phases such as sediments, soils, and food.

**REFERENCES AND NOTES**


