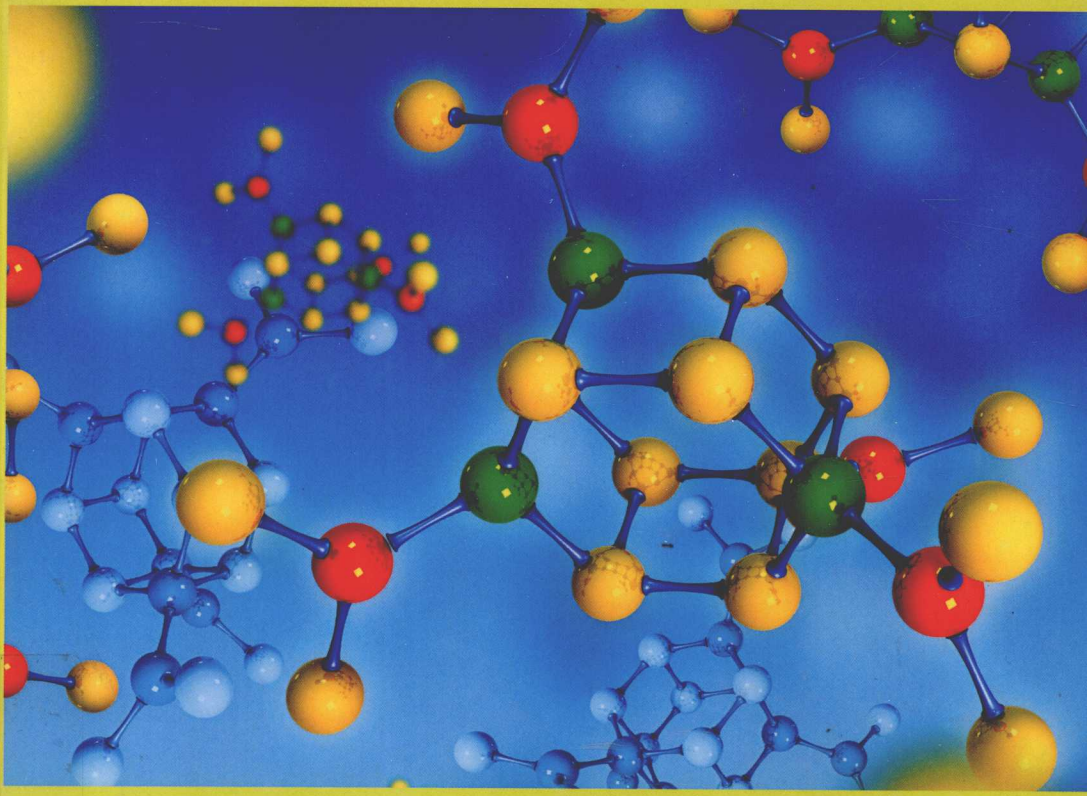
Fundamental QSARs for Metal Ions



John D. Walker
Michael C. Newman
Monica Enache

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John D. Walker
Michael C. Newman
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Preface

The idea for writing *Fundamental QSARs for Metal Ions* was inspired by: (1) reading many of the publications from Michael Newman's laboratory on quantitative ion character-activity relationships (QICARs), and (2) co-authoring a 2003 review with Monica Enache on quantitative cation-activity relationships (QCARs) for metal ions. We use the term *quantitative structure-activity relationship* (QSAR) in the title because it's the more universally recognized acronym. However, the terms QCARs, QSARs, and QICARs are used interchangeably throughout the book, depending upon whose publication we're discussing.

When Monica, Michael, and I discussed writing the book, we knew it would be a challenging task to write the first book on QSARs for metal ions. At Monica's suggestion, we solicited the contributions of one chapter coauthor and two chapter authors who provided chemical properties of metal ions and descriptors to predict metal–ligand binding. Monica coauthored Chapter 2 with Maria Pele* and translated parts of Chapters 3 and 4 from Romanian to English. Chapter 3 was written by Valentina Uivarosi† and Chapter 4 was written by Laszlo Tarko.‡ Michael wrote Chapters 1 and 8 and provided extensive constructive comments on Chapters 2–7. I wrote Chapters 5, 6, and 7 and reviewed Chapters 1–4 and 8.

Fundamental QSARs for Metal Ions was designed to provide guidance and information so that the regulatory and regulated communities could develop QSARs for metal ions as they do now for organic chemicals. Chapter 1 provides a historical perspective and introduction to developing QSARs for metal ions. Chapter 2 explains the electronic structures and atomic parameters of metals essential to understanding differences in toxicity. Chapter 3 describes the chemical properties of metals that have been and can be used to develop QSARs for metal ions. Chapter 4 illustrates the descriptors needed to develop metal ion–ligand binding QSARs. Chapter 5 discusses the 97 QSARs for metal ions developed from 1972 to 2003 and the 183 QSARs for metal ions that were developed from 2004 to 2011, since our 2003 QCARs review. Chapter 6 explains the differences between QSARs for metal ions and biotic ligand models. Chapter 7 lists the regulatory limits of metals and provides examples of regulatory applications. Chapter 8 illustrates how to construct QSARs for metal ions.

* Maria Pele, Ph.D., Professor, The University of Agricultural Sciences and Veterinary Medicine of Bucharest, Bd. Marasti 59, Sector 1, Bucharest, Romania.

† Valentina Uivarosi, Ph.D., Faculty of Pharmacy, Department of Inorganic Chemistry, University of Medicine and Pharmacy "Carol Davila," Bucharest, Romania.

‡ Laszlo Tarko, Ph.D., Romanian Academy Center of Organic Chemistry "Costin D. Nenitzescu," Sector 6, Splaiul Independentei 202 B, Bucharest, Romania.

About the Authors

John D. Walker has 44 years of professional academic, industrial and government experience in environmental toxicology and chemistry. Since 1989 he has been Director of the Toxic Substances Control Act Interagency Testing Committee (ITC), The ITC is an independent advisory committee to the U.S. Environmental Protection Agency (U.S. EPA) Administrator with representatives from 14 U.S. Government organizations. The ITC's statutory responsibility is to identify industrial chemicals that are likely to harm humans or the environment and recommend them for testing to develop data needed to assess their risks. Prior to being selected as the ITC's Director John was a senior scientist with the U.S. EPA, a regulatory toxicologist with the U.S. Food and Drug Administration, an environmental scientist with Lockheed Martin and a Research Associate at the University of Maryland.

John received his bachelor's degree in chemistry and biology magna cum laude from Kent State University where he was elected to Phi Beta Kappa. He studied microbiology at the University of Dayton where he was elected to Sigma Xi and studied aquatic toxicology at the Ohio State University's Franz T. Stone Laboratory while earning his Ph.D. His M.P.H. is from the Johns Hopkins University School of Public Health.

John is a Charter Member of the Society of Environmental Toxicology and Chemistry (SETAC), an Emeritus Member of the American Society for Microbiology and the American Academy of Microbiology and a former Editor of SETAC's International Journal, *Environmental Toxicology and Chemistry.*

John co-authored the *Laboratory Manual for Marine Microbiology* and edited the book, *QSARs for Pollution Prevention, Toxicity Screening, Risk Assessment and Web Applications.* He has authored or co-authored 160 peer-reviewed publications and has written 140 abstracts of presentations for national and international professional society meetings. John was the first recipient of the American Fisheries Society/U.S. EPA Science Achievement Award in Biology/Ecology and has been awarded 5 U.S. EPA Bronze medals. He was awarded the U.S. EPA's Unsung Hero Award for his work with Special Olympics. John is married with 4 children and 2 grandchildren.

Michael C. Newman is currently the A. Marshall Acuff Jr. Professor of Marine Science at the College of William and Mary's Virginia Institute of Marine Science, where he also served as Dean of Graduate Studies for the School of Marine Sciences from 1999 to 2002. Previously, he was a faculty member at the University of Georgia's Savannah River Ecology Laboratory. His research interests include quantitative ecotoxicology, environmental statistics, risk assessment, population effects of contaminants, metal chemistry and effects, and bioaccumulation and biomagnification modeling. In addition to more than 125 articles, he has authored 5 books and edited another 6 on these topics. The English edition and Mandarin and Turkish translations of *Fundamentals of Ecotoxicology* have

been adopted widely as the textbook for introductory ecotoxicology courses. He has taught at universities throughout the world, including the College of William and Mary, University of California–San Diego, University of Georgia, University of South Carolina, Jagiellonian University (Poland), University of Antwerp (Belgium), University of Hong Kong, University of Joensuu (Finland), University of Koblenz–Landau (Germany), University of Technology–Sydney (Australia), Royal Holloway University of London (UK), Central China Normal University, and Xiamen University (China). He has served numerous international, national, and regional organizations, including the OECD, U.S. EPA Science Advisory Board, Hong Kong Areas of Excellence Committee, and the U.S. National Academy of Science NRC. In 2004, the Society of Environmental Toxicology and Chemistry awarded him its Founder's Award, "the highest SETAC award, given to a person with an outstanding career who has made a clearly identifiable contribution in the environmental sciences."

Monica Enache has 13 years of professional academic experience in Biology. Since 1999 she has been working at the Faculty of Biotechnology of the University of Agricultural Sciences and Veterinary Medicine of Bucharest, Romania. Prior to joining the faculty she carried out her PhD degree in Liverpool John Moores University (UK), and received her Bachelor of Science degree from the Faculty of Biology of the University of Bucharest (Romania). She is currently a member of the National Society of Cell Biology in Romania, and has authored or co-authored 10 publications and 14 abstracts for presentations at national or international scientific meetings.

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1 Introduction

1.1 THE CONCEPT OF STRUCTURE–ACTIVITY RELATIONSHIPS (SARS)

> SAR resides at the intersection of biology, chemistry, and statistics.
>
> **McKinney et al. (2000, p. 9)**

McKinney et al. (2000) identified the essential steps in generating SARs. It is critical at the beginning to identify the mechanism underpinning the bioactivity of interest. Once the underpinnings are defined, the relevant toxicants and their relevant qualities can be identified with the intention of using them to understand and predict trends within the toxicant class. Next, a qualitative or quantitative approach that relates toxicant qualities to bioactivity is formulated. Approaches range from simple dichotomous categorizations to complex quantitative models generated with a variety of statistical techniques. Such SARs or quantitative SARs (QSARs) are relevant to the specified toxicant class and bioactivity. Additional SARs might be needed to address other classes or activities.

The QSAR approach for organic compounds is well established in contrast to the nascent approach for inorganic chemicals such as metal ions. As a late nineteenth-century QSAR example, the Meyer-Overton rule related anesthetic potency to its oil–water or oil–air partition coefficient. This theme of relating organic compound bioactivity or accumulation to lipophilicity still dominates much of QSAR literature about nonpolar organic contaminants. There are numerous cases where additional qualities based on other molecular structures or properties of organic compounds are included to develop QSARs for different organic contaminant classes. These qualities are often quantified in metrics of nucleophilicity, electrophilicity, molecular topology, and steric qualities (Newman and Clements 2008). QSARs based on lipophilicity, nucleophilicity, electrophilicity, molecular topology, or steric qualities have been developed for pollution prevention, toxicity screening, risk assessment, and web applications (Walker 2003).

In contrast, qualitative rules such as the d-orbital electron-based Irving-Williams series (Brezonik et al. 1991) are well established for ordering the relative bioactivities of subsets of metals, but quantitative relationships for metal ions have remained inexplicably underdeveloped in toxicology and risk assessment (Newman et al. 1998; Walker and Hickey 2000). Fortunately, this underdevelopment is now recognized as such and is steadily being resolved, as illustrated by the studies described in Chapter 5.

1.2 METALS IN THE MOLECULAR ENVIRONMENT

Metals can be classified based on an array of qualities. Some are more useful than others for quantitatively predicting intermetal differences in bioactivity. Following the lead of numerous authors, most notably Nieboer and Richardson (1980), this

treatment will focus on classification schemes that link biological mode of action to coordination chemistry.

There are several candidate metal classification schemes to employ for SAR and QSAR generation (Duffus 2002). The easiest to eliminate at the onset is classification based on whether the metal is an unstable or stable nuclide. This classification is irrelevant because our intent is not prediction of effects arising from different types of ionizing radiations. It is prediction of adverse effects from chemical interaction between metal and organism. Classification based on natural abundances such as *bulk*, *abundant*, or *trace* elements is unhelpful because we wish to make predictions for toxicological effects at unnatural, as well as natural, concentrations. However, there are cases in which natural abundance or natural occurrence information can provide valuable insight, as exemplified by the studies of Fisher (1986) and Walker et al. (2007), respectively. Another general classification of metals is the dichotomous division of metals as either being heavy or light metals. The general cutoff between these two groupings (circa 4 g cm^{-3}) has been applied loosely to highlight the toxicity of many heavier metals. Obviously, a dichotomous schema has minimal utility here, especially for creating QSARs. At a slightly finer scale, Blake (1884) did note more than a century ago a correlation between atomic number and metal toxicity. Conforming to the Irving-Williams series, toxicity to mice increased progressively with atomic numbers from manganese (atomic number 25, density 7.43) to copper (atomic number 29, density 8.96) (Jones and Vaughn 1978), but this increase also corresponded with the progressive addition of d-orbital electrons from $[Ar]3d^5 4s^2$ to $[Ar]3d^{10}4s^1$. Such a scheme based on density or atomic number does not incorporate important periodicities influencing metal toxicity. A schema framed around the periodic table seems more amenable because metal binding to critical biochemicals can easily be related to the classic periodicities therein. Certainly, trends in the nature and occupation of the outer valence shell can be discussed starting from this classic vantage, e.g., qualities of d- versus s- and p-block elements (Barrett 2002; Walker et al. 2003). However, this approach requires extension to generate related quantitative metrics of binding tendencies. For example, zinc ($[Ar]3d^{10}4s^2$) was less toxic in the above progression (Jones and Vaughn 1978) than might have been anticipated based on atomic number, density, or the number of d-orbital elections alone. With the maturation of coordination chemistry as a predictive science, relevant quantitative metrics have emerged that combine several metal ion properties into directly useful metrics. Continuing the example, the empirical softness index (σ_p) described later conveniently resolves the inconsistency just noted for zinc toxicity. These schemes framed on classic periodicity-related binding tendencies are favored here.

> The primary purpose of classifying [metal ions] in (a), or hard, and (b) or soft, is to correlate a large mass of experimental facts. All the criteria used for the classification are thus purely empirical; they simply express the very different chemical behavior of various [metal ions].
>
> **Ahrland (1968, p. 118)**

TABLE 1.1
Classification of Metal Ions According to Nieboer and Richardson (1980)

Metal Ion Class	Metal Ions
b	Au^{+}, Ag^{+}, Cu^{+}, Tl^{+}
	Hg^{2+}, Pd^{2+}, Pt^{2+}
	Bi^{3+}, Tl^{3+}
Intermediate or borderline	Cd^{2+}, Co^{2+}, Cr^{2+}, Cu^{2+}, Fe^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Sn^{2+}, Ti^{2+}, V^{2+}, Zn^{2+}
	Fe^{3+}, Ga^{3+}, In^{3+}
a	Cs^{+}, K^{+}, Li^{+}, Na^{+}
	Ba^{2+}, Be^{2+}, Ca^{2+}, Mg^{2+}, Sr^{2+}
	Al^{3+}, Gd^{3+}, La^{3+}, Lu^{3+}, Sc^{3+}, Y^{3+}

Note: The actinides and lanthanides are class (a) metals. Although placed in this table as an intermediate metal ion, Pb^{2+} tends toward class (b) more than most intermediate metal divalent ions in that part of this table. Cd^{2+} also is classified as being along the line between class (b) and intermediate metal ions.

Pearson (1963) and Ahrland (1968) developed the hard and soft acids and bases (HSAB) concept that fulfills many of the practical requirements for metal ion SARs and QSARs. Their approach was to quantify differences in metal ion bond stability during complexation with different ligand atoms. The electrophilic metal ion was envisioned as a Lewis acid and the nucleophilic donor atom of the ligand as a Lewis base.* Class (a) and (b) metals were designated hard and soft Lewis acids, respectively. The soft/hard facet of HSAB theory refers to how readily the outer valence shell deforms during interaction between the metal ion and ligand donor atom. This quality of metal ions generally corresponds to nonpolarizable (hard, class [a]) and polarizable† (soft, class [b]) during interaction with donor atoms of ligands.

The class (a) and (b) metals are clustered predictably in the periodic table, with intermediate (borderline) metals being found between these clusters. The exact borders for these classes of metals vary in the published literature because the tendencies used to separate the metals are continuous and a discrete classification is partially arbitrary.

The widely applied Nieboer and Richardson (1980) tabulation of these metal ions classes is summarized in Table 1.1. The general trend in bond stability of the class (a) metal ions with various ligand donor atoms is O>N>S and that for class (b) metal ions is S>N>O (Nieboer and Richardson 1980). Borderline metal ions are more complex, having binding tendencies intermediate between class (a) and (b) metals. Interactions between the hard class (a) metal ions and ligands tend to be ionic in

* Recollect that a Lewis acid is a species that can accept an electron pair and a Lewis base is one that can donate an electron pair.

† A polar bond is one in which a dipole is formed along the bond axis. Polarizability in this treatment generally corresponds with the readiness of the valance shell to deform during metal-ligand interaction.

nature and those for class (b) tend to be covalent. Those of intermediate metal ions vary in degrees in the covalent nature to their bonds with ligands.

The coordination chemistry-based approach for qualitatively predicting trends in metal ion bioactivities has been applied successfully for several decades. In the early 1960s, Shaw (1961) drew from the field of coordination chemistry to relate metal toxicity to metal–ligand bond stabilities. Using the then-maturing HSAB theory, Jones and Vaughn (1978) related toxicity directly to a continuous metric of metal ion softness, σ_p. Williams and Turner (1981) extended this approach by adding more toxicity data and considering mono-, di- and trivalent metal ions. This general approach continues to be expanded and refined to generate metal ion QSARs.

1.3 METALS IN AND EFFECT ON WHOLE ORGANISMS

Coordination chemistry directly influences metal–biological interactions, although metal essentiality can introduce additional features (Fraústo de Silva and Williams 1993). Relevant interactions include adsorption to biological surfaces, bioaccumulation, and toxicological effect. This chapter broadly describes these biological phenomena and, through examples, relates them to metal coordination chemistry. Such relationships between metal ion characteristics and bioactivity were referred to as *ion character-activity relationships* (ICARs) by Newman and coworkers (e.g., Ownby and Newman 2003). The quantitative rendering of these relationships has been called, alternatively, *quantitative ICARs* (QICARS) by Newman et al. (1998) and *quantitative cationic-activity relationships* (QCARs) by Walker et al. (2003). ICARs will be discussed in the remainder of this chapter, while detailed discussions of QCARs and QICARs are presented in later chapters.

> Many attempts have been made to correlate the physiological action of the elements with their physical or chemical properties, but with only partial success.
>
> **Mathews (1904, p. 290)**

> [T]he degree of toxicity of ions is largely determined by their affinity for their electrical charges, this affinity determining the readiness with which they tend to abandon the ionic state to enter into chemical combination with protoplasmic compounds.
>
> **Erichsen Jones (1940, p. 435)**

> [T]he fungostatic action of metal cations is related to the strength of covalent binding to surface ionogenic groups on the cell ...
>
> **Somers (1961, p. 246)**

> The results of this investigation ... establish a toxicity sequence ... that is of very general significance in aquatic biology and one that is also firmly based on the principles of co-ordination chemistry.
>
> **Shaw (1961, p. 755)**

> Quantitative ion character-activity relationships can be developed for a range of effects based on metal–ligand binding theory.
>
> **Newman et al. (1998, p. 1423)**

> Developing and validating Quantitative Cationic Activity Relationships or (Q)CARs to predict the toxicity [of] metals is challenging because of issues associated with metal speciation, complexation and interactions within biological systems and the media used to study these interactions.
>
> **Walker et al. (2003, p. 1916)**

As reflected in these quotes, the idea that metal ion biological activity is relatable to coordination chemistry is more than a century old. What is new is our emerging capability to quantitatively predict metal–biological activity with coordination chemistry-based metrics. Our understanding of coordination chemistry has advanced substantially, bringing along with it an assortment of convenient metrics for quantifying differences in metal chemistries. Although the pioneering work of Alfred Werner that began the field of coordination chemistry took place a century ago, the HSAB concepts that permeate discussions here and in other chapters came together only in the last half of the twentieth century (e.g., Pearson 1963, 1966). Hard and soft acids and bases theory now has evolved to such an extent that it is applied to develop both organic and inorganic QSARs (Carlson 1990). An array of potential physicochemical metrics has emerged with more refinements made every year. They are actively being assessed for their relative advantages in facilitating quantitative prediction of metal bioactivity (e.g., Kaiser 1980). Reviews by Newman et al. (1998), Ownby and Newman (2003), and Walker et al. (2003) reconfirm the viability of predicting metal activity with metal ion coordination chemistry metrics. Studies such as those of Wolterbeek and Verberg (2001), Kinraide and Yermiyahu (2007), and Kinraide (2009) enhance their potential each year by comparing and refining metrics. Complementing this growth in physicochemical metrics is the increasingly comprehensive and sound effects database available for use in quantitative models. Enough progress had been made as we enter the new millennium that general metal selection approaches for developing these relationships are beginning to emerge (e.g., Wolterbeek and Verburg 2001). It is the explicit goal of this book to synthesize this recent work, and in so doing, facilitate further advancement toward establishing powerful QSARs for metals.

1.3.1 Accumulation in the Organism

A metal ion must interact with a biological surface before being taken up and having an effect. Such interactions can be conveniently modeled with the Langmuir model.

$$n = \frac{KCM}{1 + KC} \tag{1.1}$$

where n is the measured amount of metal adsorbed per unit of adsorbent mass, C is the measured equilibrium dissolved metal concentration, M is the estimated