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Effect doses for protection of human health predicted from physicochemical properties of metals/metalloids☆

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ABSTRACT

Effect doses (EDs) of metals/metalloids, usually obtained from toxicological experiments are required for developing environmental quality criteria/standards for use in assessment of hazard or risks. However, because in vivo tests are time-consuming, costly and sometimes impossible to conduct, among more than 60 metals/metalloids, there are sufficient data for development of EDs for only approximately 25 metals/metalloids. Hence, it was deemed a challenge to derive EDs for additional metals by use of alternative methods. This study found significant relationships between EDs and physicochemical parameters for twenty-five metals/metalloids. Elements were divided into three classes and then three individual empirical models were developed based on the most relevant parameters for each class. These parameters included log-βn, ΔE_0 and $X_m^2 r$, respectively ($R^2 = 0.988, 0.839, 0.871$, $P < 0.01$). Those models can satisfactorily predict EDs for another 25 metals/metalloids. Here, these alternative models for deriving thresholds of toxicity that could be used to perform preliminarily, screen-level health assessments for metals are presented.

1. Introduction

Contamination of various components of the environment by elements, including some metals or metalloids can be serious and exposure to those elements can affect the health of humans. For centuries, several metals have been known to be toxic to humans (Friberg et al., 1979), especially in urban areas and locations where minerals are being mined, smelted or otherwise extracted or used in industrial processes. Because bioassays with model animals and acceptable human epidemiological studies are often costly and lengthy the information that can be used to derive standards is sparse. Thus, accurately assessing the risks of exposures to metals/metalloids in the environment on health of humans and the formulation of relevant pollution control plans and policy is challenging. There was an outstanding need for better data from which to develop acceptable standards for protection of health of humans and in particular better methods for assessing the significance of relevant concentrations of metals/metalloids to be developed (Preston, 1973; Wu et al., 2010).

Effect doses (EDs) are commonly used as the scientific foundation for assessment of risks to health of humans and efficient management of those risks. ED is the threshold dose for a measurement endpoint of toxicity, derived in an animal bioassay or an acceptable human epidemiological study. The most commonly used toxic endpoints for EDs are no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL) and the benchmark dose (BMD) (U.S.EPA, 2002). In general, values for NOAEL and LOAEL are derived from data obtained during toxicological experiments. The BMD is calculated based on all dose-response data within an adverse effect compared to background

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(U.S.EPA, 1995). These endpoints can include effects of individual elements on animals during laboratory studies and clinical or epidemiological studies of health of humans and also determining environmental quality criteria/standards and assessing risks to health of humans (Wu et al., 2010; U.S.EPA, 2002).

However, due to the lack of data on toxic potencies of metals, EDs for protecting human health have been recommended by the USEPA for only twenty-five metals or metalloids, while EDs for more than 50 other metals have not yet been given by regulatory jurisdictions. The implications of this are several. First, tests using standardized methods are needed to obtain data for model animals that can be used to derive EDs and conduct assessments of risks to humans (Demchuk et al., 2008). This information is not available for many species, such as rare or endangered species, which are often key species to be protected. Second, for some nonessential transition metals it is difficult to accurately determine forms and thus bioavailability in complex biological systems. Third, most of the lanthanide and actinide metals are not suitable for clinical tests because they are usually rare and have greater toxic potencies. Radioactive elements do not conform to the original purposes of environmental protection and thus because the critical mode of toxic action is different, they are considered separately. Therefore, because prediction of potential adverse effects of metals or metalloids on the health of humans depends on availability of EDs, effective predictive models are desirable.

Developing better predictive models is the future of integrated strategies of toxicology (Hartung, 2009). The Agency for Toxic Substances and Disease Registry (ATSDR) has begun to develop and apply advanced computational models to enhance traditional toxicological methods and obtain EDs or toxicity for more chemicals (Demchuk et al., 2008). Most studies have developed toxic potencies for organic chemicals such as PCDEs and persistent organic pollutants (POPs) (Domingo, 2006; Gramatica and Papa, 2007), while there is less research on inorganic chemicals, such as metals. Chemical informatics, such as quantitative structure activity relationships (QSARs), have been used to predict toxicity or sublethal effects (Zhu et al., 2009). QSARs are widely established in pharmacology and toxicology for organic molecules, while analogous quantitative ion character-activity relationships (QICARs) have been proposed to predict toxic potencies, for effects of metal ions on ecosystems and humans (Newman and McCloskey, 1996; Newman et al., 1998; Walker et al., 2003). Currently, QSAR methods, incorporated into ATSDR documents (Demchuk et al., 2011), have been used to robustly predict various toxicity endpoints such as NOAEL and LOAEL of organic compounds.

Metals or metalloids with similar electronic structures can have similar physicochemical properties, which, in turn can determine mechanisms of toxicity (Shaw, 1961). Critical mechanisms of toxicities for metals are often associated with their electronic structures and key physicochemical properties, crystal lattice, binding affinity with biological macromolecular ligands (Ochiai, 1995). Hence, more than twenty physicochemical parameters of metal ions have been proposed to predict biological activities. These include a range of parameters that relate to size and charge densities of atoms or their crystal lattice structures in bulk or in associations with other atoms. Specifically, these parameters that are either first or second principles, include softness, hydrolysis, ionization, coordination, and geometric characteristics of metal ions (Walker et al., 2003). It has been demonstrated that effects of metals on the health of humans depend on their properties and how they are related to functions (Zhu et al., 2009; Toropova et al., 2014; Rupp et al., 2010). There was a crucial study that applied QICAR models to predict disease in humans that exhibited similar properties (Meng et al., 2013). In fact, a close relationship was observed between toxicity of metals to humans and physical and chemical properties of metal ions (Meng et al., 2013). However, QSARs to predict dose-response relationships for metals or metalloids are still rarely used in assessments of risks to health of humans (Wang et al., 2012). Thus, it is rare and would be significant if EDs or toxicity of metals or metalloids to humans could be predicted by use of QICARs. The purpose of this study was to investigate relationships between EDs of metals or metalloids recommended by USEPA and their physicochemical properties by use of QICARs and statistical analysis. A further goal was to use these relationships to develop several predictive models based on complex behavior of metals or metalloids.

To demonstrate this structural property-based approach, the present study collected data for all twenty-five metals or metalloids for which EDs have been recommended by USEPA and established three empirical, quantitative, linear free energy models based on the inherent physical and chemical properties of metals. After rigorous tests of internal stability and external predictive abilities, the three models were used to predict three classes of EDs for another 25 metals in the fourth, fifth and sixth periods of the periodic table, including the Lanthanide and Actinide Series. Predicted values were compared with toxicity data from the literature, so as the robustness of the predictive model were examined.

2. Materials and methods

2.1. EDs data sets

Data selected were all appropriate EDs ($mg \cdot kg^{-1} \cdot day^{-1}$) of twenty five metals or metalloids from USEPA databases of Integrated Risk Information System (IRIS) (http://www.epa.gov/IRIS/), ATSDR (http://www.atsdr.cdc.gov/) and Provisional Peer-Reviewed Toxicity Value (PPRTV) (http://hhpprtv.ornl.gov/quickview/pprtv_compare.php) (Table 1). Data were assessed for usability based on several criteria: (1) data on toxic potencies to cause adverse effects in humans were preferred; (2) if data for observations on humans or information on harmful effects observed in exposed populations of humans were not available, data on toxicity to animal models were chosen as supplementary information; (3) the toxicity data from humans including epidemiological data could be used for evaluations of dose - effect relationships as well as selection of appropriate measurement and assessment endpoints; (4) when thresholds for effects on health are derived from use of an animal bioassay, such as mice, rats, dogs, rabbits, pigs and other animals or an acceptable human epidemiological study or clinical research appropriate application factors need to be applied. Thus, the inference process for equivalent doses of toxic effects from animal to human was avoided. The twenty-five metals or metalloids collected include silver (Ag), aluminum (Al), arsenic (As(III)), barium (Ba), beryllium (Be), cadmium (Cd), cobalt (Co), chromium (Cr(III) and Cr(VI)), copper (Cu), iron (Fe(III)), mercury (Hg), lithium (Li), lutetium (Lu), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin(Sn), strontium (Sr), thallium (Tl), uranium (U), vanadium (V), zinc (Zn) and zirconium (Zr). For higher valency ions, such as Cr(VI) and V, EDs derived by USEPA used K_2CrO_4 (MacKenzie et al., 1958) and sodium metavanadate ($NaVO_3$) (Boscolo et al., 1994) in their experiments, which might occur as oxyanions in the water. But in the present study free metal ions rather than its oxyanions were considered. In order to establish a validated model, 25 metals or metalloids were split into a training set of nineteen metals and a validation set containing six metals (Table 1). The splitting criteria were as follows: (1) select metals for which values of thirty one physical and chemical parameters were available into the training set; (2) place a different group of elements into the validation set; (3) the metals of the training and validation sets came from three sources (IRIS, PPRTV, ATSDR)as

Table 1
Effect doses (EDs) of 25 metals or metalloids. T and V represent the metal divided into the training set and validation set, respectively.

Atomic number	Metals or metalloids	Databases	Effect Doses ($mg \cdot kg^{-1} \cdot day^{-1}$)	Endpoints	Sets
3	Li	PPRTV	2.1	LOAEL	T
4	Be	ATSDR	0.6	NOAEL	T
13	Al	IRIS	0.043	LOAEL	T
24	Cr(VI)	IRIS	2.5	NOAEL	T
25	Mn	IRIS	0.14	NOAEL	T
26	Fe(III)	PPRTV	1	LOAEL	T
27	Co	PPRTV	1	LOAEL	T
28	Ni	IRIS	5	NOAEL	T
29	Cu	ATSDR	0.03	NOAEL	T
30	Zn	IRIS	0.91	LOAEL	T
33	As(III)	IRIS	0.0008	NOAEL	T
34	Se	IRIS	0.015	NOAEL	T
38	Sr	IRIS	190	NOAEL	T
47	Ag	IRIS	0.014	LOAEL	T
48	Cd	IRIS	0.005	NOAEL	T
51	Sb	IRIS	0.35	LOAEL	T
56	Ba	IRIS	63	BMD	T
80	Hg	IRIS	0.392	LOAEL	T
81	Tl	PPRTV	0.04	NOAEL	T
24	Cr(III)	IRIS	1468	NOAEL	T
23	V	PPRTV	0.22	NOAEL	V
40	Zr	PPRTV	0.79	LOAEL	V
42	Mo(VI)	IRIS	0.14	LOAEL	V
50	Sn	ATSDR MRL	0.025	NOAEL	V
71	Lu	PPRTV	504	NOAEL	V
92	U	IRIS	2.8	LOAEL	V

much as possible.

2.2. Physicochemical properties data sets and preliminary correlation analysis

Based on results of several previous studies (McCloskey et al., 1996; Pyykkö and Atsumi, 2009; Dean, 1990; Wolterbeek and Verburg, 2001; G.I.o. Geochemistry, 1981; Haynes, 2013; Schwerdtfeger, 2014), thirty-one parameters were selected to characterize various physical and chemical properties of metal ions, including parameters of the basic geometry characteristics, electrical charges, partition coefficients, thermodynamic, hardness and redox capacities of metal ions (Table S1). Some of these parameters such as Z/r, Z/r^2 and Z^2/r were recalculated to fit the current model. Because the variables used to describe environmental concentrations are often log-normally distributed raw data were transformed to the natural logarithm and standardized before use in analyses (Qian, 2011). Pair wise correlations between 31 parameters and EDs of target metals recommended by the USEPA (Table S2) were investigated by use of *Pearson* correlation analysis.

2.3. Cluster analysis

Based on different categories of objects, cluster analyses were divided into *R*-type and *Q*-type. The subject of *R*-type cluster analysis is variables (indexes), while the subject of *Q*-type is samples (Gao, 2001). *R*-type cluster analysis can be used to obtain good- or poor-relationships between variables and combinations of variables, and based on the resulting classifications a few key variables were selected for use in further analyses such as *Q*-type cluster analysis and regression analysis. *R*-type cluster analysis was carried out based on measures of similarity between EDs of metals or metalloids and thirty-one physicochemical properties. *Q*-type cluster analysis can be used to classify samples in order to find the metals that have similar "features". In the present study, *R*-type cluster analysis was used to cluster thirty-one physicochemical parameters of metal ions, to find the most relevant relationships between ED values and physicochemical properties. Twenty-five ED values of metals were classified by the obtained physicochemical parameters by use of *Q*-type cluster analysis. To ensure different dimensions or different ranges of data could be compared on the same scale, parameters were standardized by subtracting the mean with resultant values divided by the standard deviation (Eq. (1)). After converting, the mean of each parameter is 0 and the standard deviation is 1, and transformed parameters are dimensionless.

$$x_{ij}^{*} = \frac{x_{ij} - \overline{x}_j}{s_j} \quad (1)$$

where $x_{ij}^{*}$is the standardized value of jth physicochemical property for the i*th* metal, $x_{ij}$is the original value of jth physicochemical property for the i*th* metal, $\overline{x}_j$is the mean of jth physicochemical property for all 25 metals, s_j is the standard deviation of jth physicochemical property for all 25 metals.

2.4. Development of predictive relationships

Empirical quantitative models were developed between parameters selected based on cluster analysis and *Pearson* correlation analysis and EDs of three classes in the training set by use of linear regression. Selected parameters and EDs were used as independent and dependent variables, respectively. The most relevant parameters were selected based on coefficients of determination (R^2), residual standard error (*RSE*), the value of F-test statistic using analysis of the linear regression fit and the level of Type I error (P) set to $\alpha < 0.05$. These parameters were also used as measures of the goodness-of-fit of QICAR models. The model with minimum RSE and maximum R^2 values was deemed the best model.

2.5. Internal validation

Predictive potentials of models were evaluated by use of internal and external validation, and then used to predict EDs of other

metals (Puzyn et al., 2011). *K*-fold cross-validation and *Y*-randomization were performed as internal validation to confirm stability and significance of the QSAR models, which could avoid over-fitting and chance correlation. The cross-validated correlation coefficient (Q^2_{cv}), which was calculated between the predicted ED values$\widehat{y}_i$ and the observed ED valuesy_i, and cross-validated root mean square error of prediction (RMSECV) were used to evaluate internal predictive power of the model (Kiralj and Ferreira, 2009). *Y*-randomization is a common method to ensure robustness of the model, the purpose of which is to test the correlation by chance between dependent and independent variables (Rücker et al., 2007). Twenty five random 'models', which did not have physical meanings, were built by use of the same independent variable and then it was correlated with the dependent variable randomly shuffled every time. The appropriate QSAR model should generally have a small correlation coefficient of *Y*-randomization (R^2_{yrand}) and a small correlation coefficient of *k*-fold cross-validation for *Y*-randomization (R^2_{yrand}). If models obtained by *Y*-randomization all have large $R^2_{yrand}$and R^2_{yrand}values, it means that the current modeling methods could not get an acceptable QICAR model for this given data set (Rücker et al., 2007).

2.6. External validation

To confirm predictive ability of models, external validation was conducted by use of validation set. The externally validated determination coefficient (Q^2_{ext}) and the root square error of prediction (RSE_{ext}) were used as the measures of predictive ability for external validation of models (Tropsha et al., 2003) (Eqs. (2) and (3)).

$$Q^2_{ext} = 1\frac{\sum_{j=1}^{m}\left(y_j^V - \widehat{y}_j^V\right)^2}{\sum_{j=1}^{m}\left(y_j^V - \overline{y}_T\right)^2} \tag{2}$$

$$RSE_{ext}\sqrt{\frac{\sum_{j=1}^{m}\left(y_j^V - \widehat{y}_j^V\right)^2}{m}} \tag{3}$$

Where $y_j^V$is the observed ED value for the *j*th metal in the validation set, $\widehat{y}_j^V$is the predicted ED value for the *j*th metal in the validation set, $\overline{y}_T$is the mean of the observed ED values in the training set, and *m* is the number of metals in the validation set.

2.7. Discriminant analysis

Discriminant analysis (DA) is a statistical method to judge classes to which samples belong, which is based on the relationship between a categorical variable and a set of interrelated variables (McLachlan, 2004). More precisely, the values are G_1, G_2, …, G_k, where k is the number of distinct classes. Sample X is known to come from k distinct classes but which is not known. DA is used to classify samples or parameters based on the existence of classes known as an a priori rule, and then the priori rule is used to classify unknown samples to classes. In addition, the Fisher discrimination method was used to classify the validation set and then predict classes to which metals belonged. The basic idea of the Fisher DA method is a projection. To overcome the "dimension curse" caused by higher dimensions, points from the higher dimensional space are projected onto a lower dimensional space, so that the data points become more intensive. Then samples of unknown class were classified based on the discriminant function then back-generation estimation was used to calculate the error rate of the discriminant function based on training samples (Johnson et al., 1992). Using results of Q-type cluster analysis as rules for classification of each metal, then the error rate was calculated to indicate accuracy of results of the DA.

2.8. Evaluation of the domain of QICAR applicability

Predictive power of models, domain of QICAR applicability was evaluated by use of William plots (Jaworska et al., 2005). The leverage value $h_{ij}$for each *j*th metal of *i*th class was calculated from the physicochemical properties matrix (X) (Eq. (4)).

$$h_{ij} = \mathbf{x_{ij}^T}\left(\mathbf{X^T X}\right)\mathbf{x_{ij}} \tag{4}$$

Where:$\mathbf{x_{ij}}$ is a row vector of a particular physicochemical property for *j*th metal. If the value of $h_{ij}$is greater than the warning h_i^*value (Eq. (5)), it indicates that the predicted ED value of this metal is located outside the optimum prediction space (Puzyn et al., 2011).

$$h_{ij}^* = \frac{3(p_i + 1)}{n_i} \tag{5}$$

Where:p_i is the number of variables used in the *i*th class QICAR model, and $n_i$is the number of metals in the *i*th class training set (Gramatica, 2007).

3. Results and discussion

3.1. General relationships between EDs and physicochemical properties

To eliminate redundancies and develop canonical models to predict EDs, pair-wise, linear regressions were used to investigate relationships between thirty-one descriptors of physicochemical properties (Table S1). Five structural parameters, including maximum complex stability constants (log-βn), covalent index ($X_m^2 r$), electrochemical potential (ΔE_0), electronegativity (X_m) and polarizability (*Pr*) were found to have reasonable correlations with EDs of nineteen metals or metalloids for which EDs were available (Table S2). EDs of those 19metals or metalloids recommended by USEPA that were included in the training set were classified by use of these five inherent physical and chemical properties of metals (Fig. S1).

The parameters, log-βn, X_m and $X_m^2 r$ were statistically but weakly and negatively correlated with log-EDs (R^2 = 0.383, P = 0.004; R^2 = 0.336, P = 0.007; R^2 = 0.315, P = 0.01). Previously, log-βn has been used to describe thermodynamic stability of cations combined with the organic ligand EDTA, CN- or SCN (Walker et al., 2012), which represents covalent binding and complexing capacity of metal ions. It was found that log-βn was negatively correlated with log-EC_{50} and this relationship was used to predict WQC of heavy metals for protecting aquatic organisms, which was consistent with the results of this study (Wu et al., 2013). X_m is an indicator that explains abilities of metal ions to attract electrons (Pauling, 1932). More active and stronger attractions of electrons by metal ions are associated with greater toxic potencies. $X_m^2 r$ comprehensively describes the relative information on covalent character of metal-ligand binding (Nieboer and Richardson, 1980) and quantifies the importance of covalent interactions relative to ionic interactions (Newman and McCloskey, 1996). Metals with larger values for $X_m^2 r$ are more easily combined with functional groups that contain N or S, which relates to greater toxicity in humans. Toxicities of metal ions are directly proportional to their ionic radii. Similarly, log-βn and $X_m^2 r$ were negatively correlated with predicted toxic potency, which was related to binding affinities and covalent interactions of metal-ligand complexes. Values of

log-βn and $X_m^2 r$ for more toxic metals, such as Hg, Ag and Tl, were greater than 18.0 and 3.5, while those for metals with lesser toxic potency, such as Sr and Ba, were less than 12 and 1.2, respectively.

On the other hand, Pr and ΔE_0 were found to be positively correlated with log-EDs. That is, ions of metals with stronger ionization energies have lesser toxic potencies to aquatic organisms ($R^2 = 0.373$, $P = 0.004$; $R^2 = 0.19$, $P = 0.055$). Polarizability (Pr) describes interactions of the electron cloud of atoms or molecules with external fields, and is usually associated with ionization energies of atoms or ions (Politzer et al., 2002). Electrochemical potential (ΔE_0), represents the absolute difference in electrochemical potential between the state of an ion and its first stable reduced state (Parr et al., 1978), which indicates that the more intense the electron clouds of metal ions, the greater the response to external fields and the stronger the ability of hydrolysis and ionization for metal ions, all of which is associated with lesser toxic potencies to humans (McCloskey et al., 1996). In addition, the softness parameter σp, which measures ability of a metal ion to donate its valence electrons (Pearson, 1963), was positively correlated with log-EDs. Consistently, σp was positively correlated with toxicity of cations for many species such as rat (Jones and Vaughn, 1978) and mouse (Williams and Turner, 1981). In conclusion, log-βn, $X_m^2 r$, ΔE_0, X_m and Pr were statistically, significantly associated with EDs in the training set, which was an improvement on recent QICARs studies. However, by observing values of coefficients of determination (R^2), the results demonstrated that none of the quantitative models presented herein were capable of directly predicting EDs of all metals or metalloids.

3.2. Empirical quantitative models for three types of metals/metalloids

In general, it is difficult to predict potencies of a range of metals or metalloids by use of any single physicochemical parameter (Can and Jianlong, 2007). Therefore, the present study assumed that different EDs of metals or metalloids might be associated with different physical and chemical properties. With this assumption, Q-type cluster analysis, based on log-βn, $X_m^2 r$, ΔE_0, X_m and Pr as independent variables, was conducted (Fig. S2). Also, in order to derive a single ED value for each metal or metalloid, because Cr(VI) was more toxic to human health and Cr(III) was measured in insoluble salts the ED of Cr(VI) was selected to represent Cr, and the ED of Cr(III) was deleted from the data set before modeling (U.S.EPA, 1998). After Q-type cluster analysis, three classes of metals were defined: (Class A) Li, Sr, Ba and Be; (Class B) Mn, Zn, Fe(III), Al, Cr(VI), Co, Ni and Sb; (Class C) Cu, Tl, Cd, Hg, Se, Ag and As(III). The classifications presented herein are consistent with those of previous studies, which indicated that Class A ions have the greatest affinity for oxygen, whereas Class C have the greatest affinity for sulfur; Class B are the transition period between Class A and Class C (Ahrland et al., 1958; Lithner, 1989).

Class-specific empirical quantitative models for the three classes of metals, which were the best fitted with log-βn, ΔE_0 and $X_m^2 r$, respectively were developed (Fig. 1). Log-βn was significantly and positively correlated ($R^2 = 0.988$, $F = 166.1$, $P = 0.0059$, RSE = 0.365) with log-EDs for Class A; ΔE_0 was significantly and negatively correlated ($R^2 = 0.839$, $F = 31.29$, $P = 0.0014$, RSE = 0.667) with log-EDs for Class B; $X_m^2 r$ was significantly and positively correlated ($R^2 = 0.871$, $F = 33.83$, $P = 0.0021$, RSE = 0.749) with log-EDs for Class C (Table 2). log-βn represents maximum binding capacity of complexation between metals and EDTA, CN^- or SCN^- (Wu et al., 2013). In particular, log-βn as an indicator of binding affinities between metals and sulfur-containing groups was useful for predicting toxic potencies of alkali metals, which was useful for discriminating among EDs in Class A. Standard reduction-oxidation

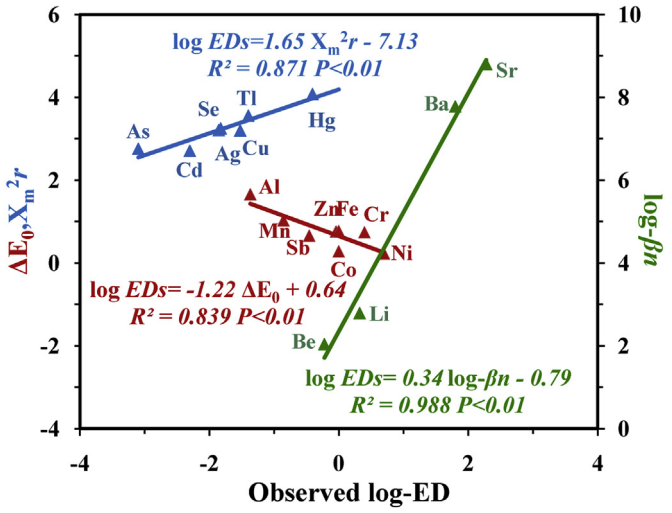

Fig. 1. Class-specific graphs of the 'best' empirical quantitative models. The green, red and blue colors represent metals or metalloids from the training set Class A, Class B and Class C, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potential (ΔE_0) is an indicator of the absolute difference in electrochemical potential between the state of an ion being in its first stable reduced state, which could represent abilities of transition metals to hydrolyze and ionize (Wolterbeek and Verburg, 2001). The covalent index, $X_m^2 r$, indicates the degree of covalent interactions in metal-ligand complexes relative to ionic interactions (Nieboer and McBryde, 1973). Results of a previous study showed that $X_m^2 r$ could be used to predict bioaccumulation of heavy metals (Veltman et al., 2008), which indicates that it is suitable to establish an empirical quantitative model with Class C since metals in that class tend to bioaccumulate.

3.3. Rigorous validation of internal stability and external predictive abilities

Only after an empirical quantitative model has been validated internally and externally is it suitable to be used to make predictions (Gramatica, 2007). OECD has proposed five principles for development of QSAR models. Models should have: (1) a defined endpoint; (2) an unambiguous algorithm; (3) a defined domain of applicability; (4) appropriate measures of goodness-of–fit, robustness and predictability; (5) a mechanistic interpretation, if possible (Gramatica, 2007; OECD, 2007). Thus, validation and verification steps were used and statistical measures of goodness-of-fit, robustness and measures of predictive ability of models were used to test accuracy of three developed empirical quantitative models. To avoid over-fitting and potential for chance correlations, k-fold cross-validation and Y-randomization were used as statistical measures of robustness. Three cross-validated correlation coefficients, Q_{cv}^2, of the final selected models were 0.9455, 0.7310 and 0.7418, respectively. The root mean square errors for cross-validation ($RMSE_{CV}$), for the three models were7.36×10^{-4}, 0.207 and7.77×10^{-2}, respectively. To avoid autocorrelations between dependent and independent variables, Y-randomization was used to confirm the $RMSE_{CV}$ measure of robustness. A total of 25 "random" models were built by use of the same independent variable and correlated with a dependent variable randomly selected for each iteration. Models obtained by Y-randomization all had small values for R_{yrand}^2 and Q_{yrand}^2 (Fig. S3), which means that the current methods of modeling were sufficient to obtain acceptable

Table 2
Regression models, where Degrees of freedom is the number of values in the regression that are free to vary in order to measure the complexity of the model, R^2 is coefficient of correlation, RSE is residual standard error and P is the level of statistical significance. The bold represent the "best" regression models of Class A, Class B and Class C, respectively.

Properties	Class	N	Degrees of Freedom	Intercept	Slope	P	R^2	Adj R^2	RSE	F
Log-β_n	**A**	**4**	**2**	**−0.79**	**0.34**	**0.0060**	**0.988**	**0.982**	**0.158**	**166.10**
	B	8	6	0.96	−0.09	0.4399	0.102	−0.047	0.684	0.68
	C	7	5	−5.29	0.18	0.4486	0.119	−0.057	0.851	0.68
X_m^2r	A	4	2	−0.34	1.42	0.7807	0.048	−0.428	1.417	0.10
	B	8	6	−0.55	0.17	0.6987	0.027	−0.136	0.712	0.16
	C	**7**	**5**	**−7.13**	**1.65**	**0.0021**	**0.871**	**0.846**	**0.325**	**33.83**
ΔE_0	A	4	2	−2.51	1.33	0.3785	0.386	0.079	1.138	1.26
	B	**8**	**6**	**0.64**	**−1.22**	**0.0014**	**0.839**	**0.812**	**0.289**	**31.29**
	C	7	5	−2.02	0.47	0.7402	0.024	−0.171	0.896	0.12
X_m	A	4	2	4.14	−2.82	0.2449	0.570	0.355	0.952	2.65
	B	8	6	−2.96	1.56	0.3156	0.167	0.028	0.659	1.20
	C	7	5	−0.80	−0.49	0.6905	0.034	−0.159	0.891	0.18
Pr	A	4	2	−0.56	0.07	0.2162	0.614	0.421	0.902	3.19
	B	8	6	−0.66	0.06	0.6898	0.028	−0.134	0.711	0.18
	C	7	5	−2.59	0.14	0.5957	0.060	−0.128	0.879	0.32

empirical quantitative models for this data set and confirms that the probabilities that the models were not obtained by chance correlations was small. External validation by comparisons of predictions of a representative set of data for which empirical values of ED were available were the only way to ensure predictive ability of the three empirical quantitative models (Dearden et al., 2009; Benigni and Bossa, 2008). A training set was classified based on the Fisher discriminant analysis (DA) and linear discriminant functions were obtained (Eqs. (6)–(8)). When back-generation was estimated the rate of errors in classification was zero.

$$Y_1 = 0.487(x_1 - \bar{x}_1) + 0.357(x_2 - \bar{x}_2) - 0.983(x_3 - \bar{x}_3) - 0.772(x_4 - \bar{x}_4) - 0.0653(x_5 - \bar{x}_5) \quad (6)$$

$$Y_2 = 0.0132(x_1 - \bar{x}_1) + 1.349(x_2 - \bar{x}_2) + 1.767(x_3 - \bar{x}_3) + 1.286(x_4 - \bar{x}_4) + 0.0279 + (x_5 - \bar{x}_5) \quad (7)$$

$$Y = 0.978Y_1 + 0.0221Y_2 \quad (8)$$

Where: x_1, x_2, x_3, x_4, x_5were log-βn, $X_m^2 r$, ΔE_0, X_m and Pr, respectively.

Six metals in the validation set were separated into two classes, A and B, according to posterior probabilities obtained by a linear, discriminant function (Eqs. (6)–(8)). Lu, Sn and U were classified as A-metals; Mo, V and Zr were classified as B-metals. Then using Classes A and B, empirical quantitative models were developed to predict log-ED values for these six metals. Nineteen predicted log-ED values were compared with log-ED values recommended by the USEPA (Fig. 2). Differences between ED values predicted by the empirical quantitative models and the EDs suggested by USEPA for the nineteen metals were within an order of magnitude, except that for Sn and Mo, which were outside this range but within one and a half orders of magnitude. These results indicated that the empirical quantitative models developed could be used to predict ED values of metals or metalloids for which empirical data is lacking, at least in preliminary assessments of hazard and risk. Also, the models would be useful for prioritization of metals for further assessment or study by collection of empirical data on toxic potencies via various pathways of exposure. When William's plot was used to evaluate optimal prediction spaces of the empirical quantitative models (Hoaglin and Welsch, 1978), among metals investigated, only the hat value for Mo exceed its $h_i^*(h_A^* = 1.5,\ h_B^* = 0.75,\ h_C^* = 6/7)$ (Fig. S4). This result suggested that predictions based on three empirical quantitative models were excellent. For Mo, which was most poorly predicted, the predicted

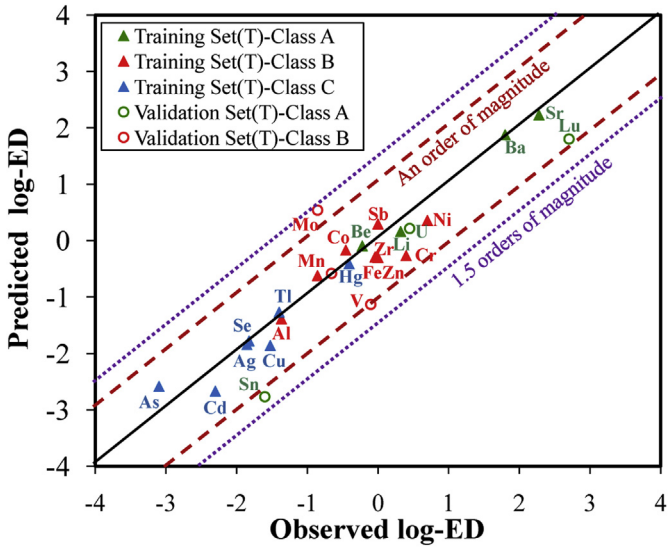

Fig. 2. Plot of observed log Effect dose (ED) versus predicted ED by use of empirical quantitative models. The green, red, and blue triangles represent values predicted for the metals or metalloids from the training set Class A, Class B and Class C, respectively; circles represent data calculated for metals from the validation sets. The distance of each symbol from the green line corresponds to its deviation from the related experimental value. The black solid line represents perfect agreement between observed and predicted values; the red dotted line represents an order of magnitude between observed and predicted values; the purple dotted line represents one and a half orders of magnitude between observed and predicted values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ED value was 3.48 mg kg^{-1} day^{-1} while the ED value (LOAEL) recommended by USEPA was 0.14 mg kg^{-1} day^{-1}. The reason for the difference was that the value of ΔE_0 used in this study was for a valence of +6, but it is not known whether a valence of +6 or +4 was used to develop the water quality criteria (WQC) guideline recommended by USEPA (IRIS) (Koval'skiy et al., 1961). Different ΔE_0 is especially important for multi-valency elements because their oxidation status affects their mobility and toxicity in aquatic environments (Antoniadis et al., 2017). Also, similar to Cr(VI) and V(V), Mo(VI) might occur as oxyanions in water, which would cause different toxic properties from those of cations. Addition of organic matter or purposefully aquatic environments might accelerate metals reduction of highly toxic to low toxic, which greatly decreases availability (Antoniadis et al., 2017). However, it is

important but more difficult to obtain toxic potencies of metal species present in a sample than the total concentrations of metals in samples. Results of previous studies have shown that ED values (LOAEL) of Mo were 1.6 mg kg^{-1} day^{-1} (Fungwe et al., 1990) and 5 mg kg^{-1} day^{-1} (Asmangulian, 1965), which both obtained by toxicity experiments. Therefore, the ED for Mo predicted by the model reported here was probably sufficiently accurate.

3.4. Prediction of effect doses for other metals

EDs of other 25 metals or metalloids that are in periods two to six of the periodic table, including the lanthanide series and the actinide series, were predicted by use of the three empirical quantitative models based on classification by use of DA (Fig. 3). Class A contains groups IA, IIA and IIIB, which is consistent with chemical behaviors of alkali metals, alkaline earth metals and IIIB (including lanthanides and actinides). Class B contains groups IVB-VIII, and IIIA, which are mainly transition metals. Class C contains mainly stable platinum group metals or metalloids, such as palladium (Pd), lead (Pb) and bismuth (Bi).

The results were similar to the results of *Q*-style cluster analysis for the training set, which indicated that classifications obtained by DA were credible and predicted values could be utilized. However, gold (Au), which is a relatively stable metal, was assigned to class B. Since the ΔE_0 value of stable Au (III) used was 1.498, which indicates that hydrolysis and ionization are different between Ag and Cu, which are in the same group. This might be the reason Au was classified as a Class B metal. The predicted value of ED for Au was 0.056 mg $kg^{-1}\cdot day^{-1}$, which was approximately the same order of magnitude as those for Cu, Ag and Hg, indicated that Au^{3+} has a relatively great toxic potency.

Since non-cancer effects of metals or metalloids can be divided into several groups according to their mechanisms of toxicity or metabolic capacities of organisms (Valko et al., 2005), the present results indicated that ions of the first group including ions of the elements including Co, Cu, Cr and Fe undergo redox-cycling reactions; the second group of metals including Cd, Ni and Hg produces the toxicity through depletion of glutathione and bonding to sulfhydryl groups of proteins; the third group is involved with both effects. The results of the present study would be additional information to reveal the mechanism governing the toxicity of metals and metalloids.

The mean ED value for Class A metals (including training and validation sets) was 14.5 mg $kg^{-1}\cdot day^{-1}$, with a standard deviation of 40.2, both of which are greater than values observed for the other two classes. This might be because predicted ED values for Sr, Ba, and Lu were as large as 169.44, 75.61, and 64.04 mg $kg^{-1}\cdot day^{-1}$, respectively. Since the chemical properties of metals within lanthanides or actinides were similar predicted EDs among lanthanides or actinides are similar, and ED values for metals in both of these groups were all less than 1.0 mg $kg^{-1}\cdot day^{-1.}$ These predicted toxic potencies were consistent with previously measured median acute, lethal (LC50) concentrations observed during one-week exposures of *Hyalella azteca* (Crustacea) collected from Lake Ontario (Borgmann et al., 2005). Predicted EDs of lanthanide metals beyond europium (Eu) in the Periodic Table are similar to those of yttrium (Y) because of the "Lanthanide contraction" (Wang and Schwarz, 1995). Mean EDs for Classes B and C were 0.52 and 0.83 mg $kg^{-1}\cdot day^{-1}$, with standard deviations of 0.79 and 2.23, respectively. This illustrated that metals or metalloids in Classes B and C have greater toxicity to humans than those in Class A. Results of a previous study (Hamilton et al., 1973) in which blood of more than 200 healthy humans in the United Kingdom were collected from 1968 to 1969 were consistent with those determined during the present study. Concentrations of most metals in each of these three classes were relatively small. For instance, concentrations of

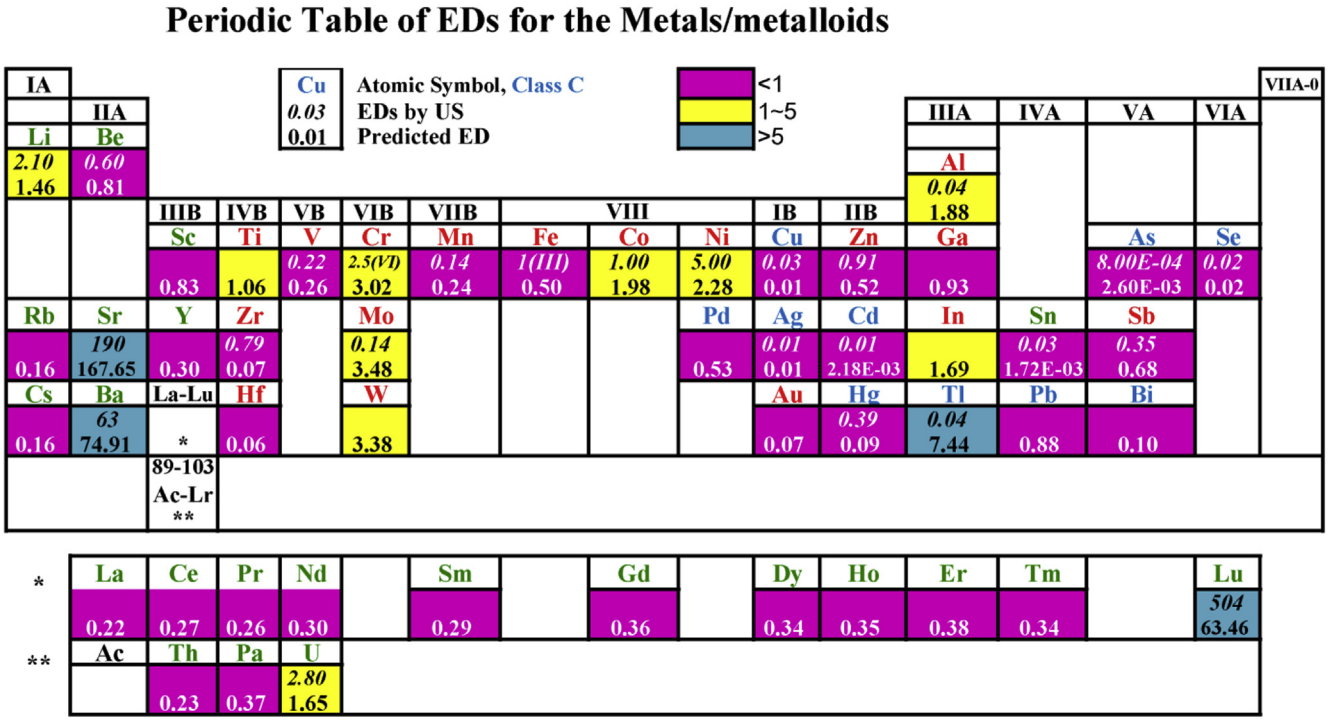

Fig. 3. Predicted effect doses (EDs). Periodic table of the elements show metals and metalloids classified into the three classes of effect doses, for which the green, red and blue colors of font represent for the metals or metalloids of Classes A, B and C. The unit of predicted values is defined as mg·$kg^{-1}\cdot day^{-1}$. The color scale of ED values show the decreasing toxic potency of metals or metalloids, ranging for pink (<1), yellow (1–5), and little blue (>5), respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

erbium (Er), holmium (Ho) and samarium (Sm) were less than 0.009 μg g^{-1} and concentrations of lanthanum (La), bismuth (Bi) and cerium (Ce) were less than 0.003 μg g^{-1} in blood of healthy humans. Predicted values of other metals were largely consistent with their toxic potencies. Based on classifications for metals obtained during this study, future toxicity testing should focus on collecting additional data for those classes for which data are sparse instead of duplicating information for the classes for which data is more complete.

Metals in class A were mainly s-block metals; metals in class B were mainly transition metals; while metals in class C were mainly stable group IB-IIB metals or metalloids. Based on Pearson's Principle of Hard and Soft Acids and Bases (HSAB) and the properties of metals including size, oxidation state, polarizability, electronegativity and binding ligands (Pearson, 1963), metal ions can be divided into soft ions (e.g., Cd, Hg, Ag and As(III)), hard ions (e.g., Li, Na, Ca and Mg) and borderline ions (e.g., Co, Ni, Cu and Zn). The new classification divided metal ions into Class A, B and C, which correspond to previous classifications of "hard ions", "borderline ions" and "soft ions", respectively. According to HSAB, most soft ions had great or intermediate toxic potencies, whereas borderline ions had lesser toxic potencies and hard ions exhibited even lesser toxic potencies. This might be the reason that three classes of metals defined based on the observed data were identified in the present study. In addition, results presented here have verified the observation (Meng et al., 2013) that seventeen metals were indeed divided into s-block metals and transition metals according to their sub-layer structures and arrangements of their electron shells, including arrangement of the electron shell and potentials for oxidation and ionization of metals to classify metals that would better represent characteristics of metals and toxic potencies of metals.

3.5. Model evaluation

Herein, this study first time divided EDs of twenty-five metals or metalloids into three classes and selected physicochemical parameters to construct relationships by use of cluster analysis and then classified another 25 metals being predicted with the discriminant analysis. The empirical quantitative models presented also improved the contributions reviewed by Wu and Mu et al. (Wu et al., 2013). First, the present study further extended the application to ED values of 50 metals or metalloids to protect human health. Second, thirty-one parameters selected were examined and used to characterize the various physical and chemical properties of metal ions. Finally, EDs of 50 metals or metalloids were predicted by three different physicochemical properties, e.g. log-βn, ΔE_0 and $X_m^2 r$, which could represent various toxic potencies of different metals or metalloids. Therefore, these quantitative and predictive models are indeed a good attempt that on behalf of a future international research development of toxicology. It could be useful when data on EDs or toxicity of metals are lacking or incomplete. Some working conditions should be taken into account to achieve reasonable predicted EDs of metals or metalloids for the protection of human health, these include (1) EDs data collected should follow the criteria in Section 2.1; (2) a training set and a validation set were needed and the splitting criteria should follow the criteria in Section 2.1; (3) physicochemical properties should be efficient and accurate; (4) models should be evaluated by use of appropriate measures of goodness-of–fit, robustness and predictability.

Although different empirical quantitative models presented can reasonably predict EDs of an additional 25 metals or metalloids for which insufficient, empirical information on toxicity is available, it was deemed necessary to improve seven areas as to obtain more reasonable predictions in future studies. They include: (1) unified different experiment designs in order to reduce errors; (2) separating metal valence when modeling might improve the model prediction accuracy; (3) need to consider the effect endpoint of different animal experiments; (4) consider effects of various compounds of metals and various anions associated with those metal ions on their toxic potencies; (5) bioavailability and affinities of metals and metalloids might be related to site-specific factors such as pH, hardness and dissolved organic carbon; (6) Cation bases and their binding conditions could be important factors affecting toxicity of metals and metalloids that must be considered; (7) further modifications for the model and development of sufficiently accurate models. Nevertheless, this study is still an important advancement for predicting toxic potencies of metals for protection of human health. The predictive models provide new approaches to predict health threshold and assess risks of metals to the health of humans even though effective factors are complex.

4. Conclusion

Models that do not depend on empirical information obtained in the present study appear to be useful for deriving ED values of metals for which few empirical toxicity data are available. More importantly, the results of the present study demonstrated correlations between physicochemical properties and EDs for three types of metals or metalloids and predicted ED values for another 25 metals in the fourth, fifth, sixth periods of the periodic table, including the Lanthanide and Actinide Series. Our findings require further confirmation, but they are deemed crucial and practical because ED values could only obtain primarily from experiments with animals or acceptable clinical or epidemiological studies of human health before, both of which are sometimes impossible to carry out experiments. Modeling approaches utilized in the present study would provide a beneficial supplement to existing methodologies for developing preliminary screening-level EDs of metals or metalloids, for which little scientific data exist to develop dose-response relationships for non-cancer effects, to establish standards and assess risks for human health.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envpol.2017.09.065.

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Supplementary data

Effect Doses for Protection of Human Health Predicted from Physicochemical Properties of Metals/metalloids

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Supplemental Tables

Table S1. Properties affecting toxicity employed in empirical quantitative models.

Abbreviation	Description	Property affecting toxicity
AN	Atomic number	Ion mass
AW	Atomic weight	Ion mass
AR	Atomic radius	Ion length scale
r	Pauling ionic radius	Ion length scale
Z	Ionic charge	Oxidation state
ΔIP	Change in ionization potential from ion to its first reduced state	Energy required for oxidation
σp	Softness coefficient	Softness
log(βn)	Logarithm of the maximum complex stability constants	Derived from the maximum strength of complexes formed between metals and EDTA, CN-, or SCN-
ΔE_0	Electrochemical potential	Tendency of an ion to be oxidized
$\log\|K_{OH}\|$	Logarithm of the first hydrolysis constant	Ability to produce hydroxyl ions
X_m	Electronegativity	Ability to attract electrons or electron density towards itself in a covalent bond
AR/AW	Electron density	Ion mass and length scale
AN/ΔIP	Atomic ionization potential	Oxidation energy
MP	Melting point	Physical properties
BP	Boiling point	Physical properties
P	Enthalpy of formation of Gaseous Atoms	Energy required for oxidation
Pr	Polarizability	Oxidation energy
IP	Ionization potential	Energy required for oxidation
D	Density	Physical properties
R-vdw	VDW radius	Ion length scale
CR	Covalent radius	Ion length scale
Cp-g	heat capacity Cp	Energy required for oxidation
Cp-m	heat capacity Cp	Energy required for oxidation
Xm-kM/P	Electronegativity	Ability to attract electrons or electron density towards itself in a covalent bond
X_m^2r	Covalent index	Covalent versus electrostatic interactions during metal-ligand binding
Z/rx	Polarization force parameter	Stability of ionic bonds

Z/r	Polarization force parameter	Stability of ionic bonds
Z/r^2	Polarization force parameter	Stability of ionic bonds
Z^2/r	Polarization force parameter	Stability of ionic bonds
Z/AR	Polarization force parameter	Stability of ionic bonds
Z/AR^2	Polarization force parameter	Stability of ionic bonds

Table S2. Pearson's correlation of 31 ion characteristics and the ED values by USEPA.

Property	*p*	Corr	R^2
Log-βn	0.004**	-0.619	0.383
Polarizability	0.004**	0.610	0.373
X_m	0.007**	-0.580	0.336
$X_m^2 r$	0.010**	-0.561	0.315
ΔE_0	0.055*	0.436	0.190
CR	0.059*	0.429	0.184
R-vdw	0.059*	0.429	0.184
σ_p	0.067*	0.418	0.174
AR	0.079*	0.402	0.161
MP	0.080*	0.401	0.161
BP	0.117	0.362	
AW	0.383	-0.206	
Z/AR^2	0.521	-0.153	
D	0.534	-0.148	
Z/rx	0.543	0.145	
AN	0.544	-0.144	
P	0.574	0.134	
AR/AW	0.597	0.126	
Z/AR	0.617	-0.119	
Cp-g	0.649	0.109	
Xm-kM/P	0.661	0.104	
r	0.765	0.071	
∆IP	0.802	0.060	
Z	0.863	-0.041	
Z/r	0.881	-0.036	
Z/r^2	0.913	-0.026	
Cp-m	0.931	0.021	
IP	0.935	0.020	
$\lvert \log K_{OH} \rvert$	0.981	0.006	
Z^2/r	0.981	0.006	
AN/∆IP	0.993	-0.002	

** means $p<0.05$.

* means $0.05<p<0.1$.

Supplemental Figures

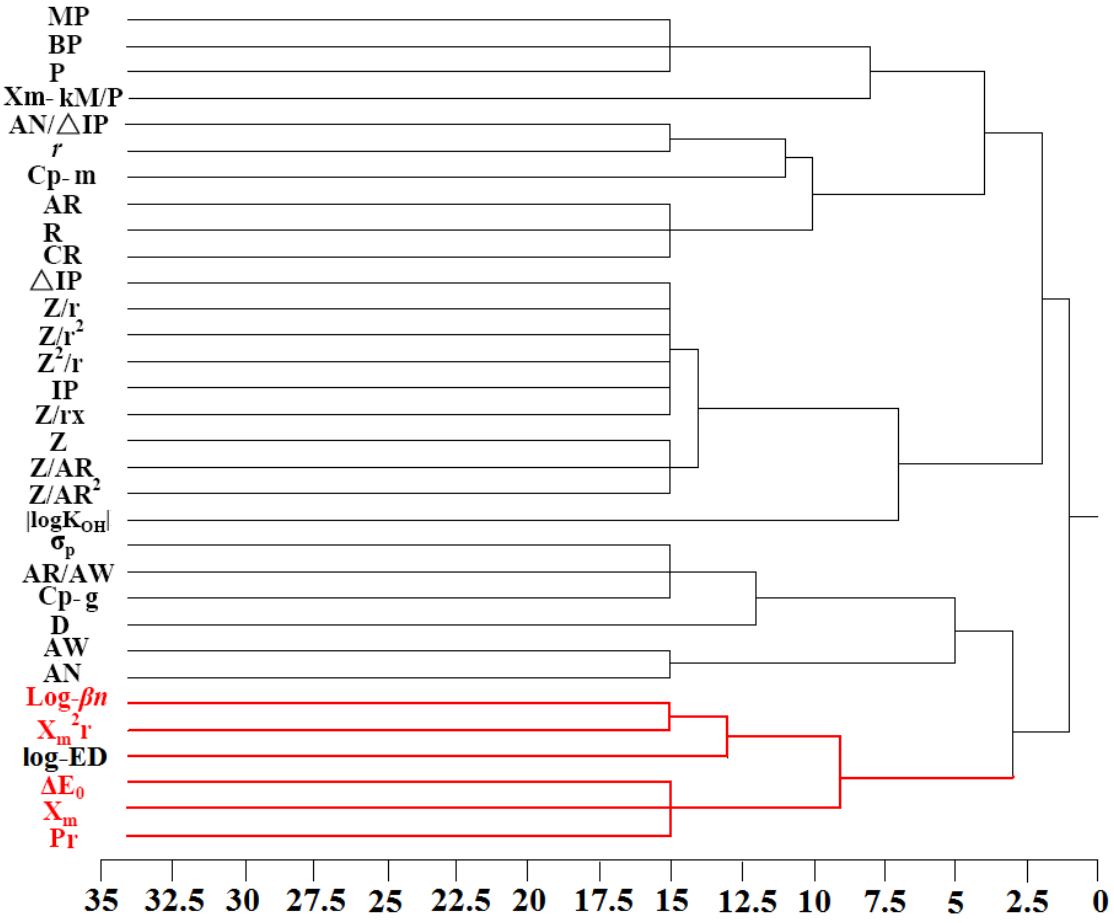

Fig. S1. R-type cluster analysis. The red coloring represents the physicochemical properties that have close relationships with log-ED.

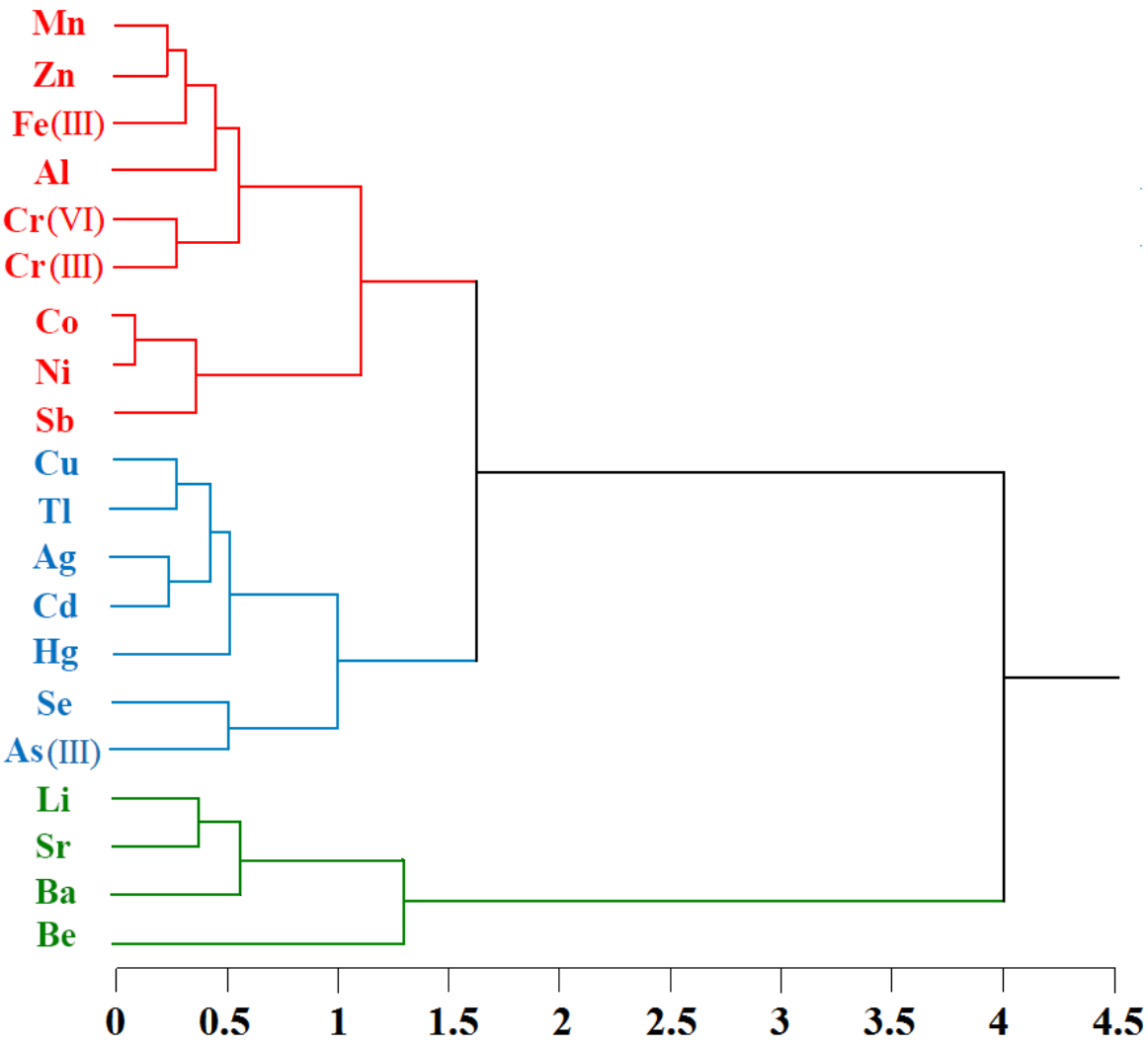

Fig. S2. Q-type cluster analysis. The green, red, and blue coloring represent the metals or metalloids from the training set Class A, Class B, and Class C, respectively.

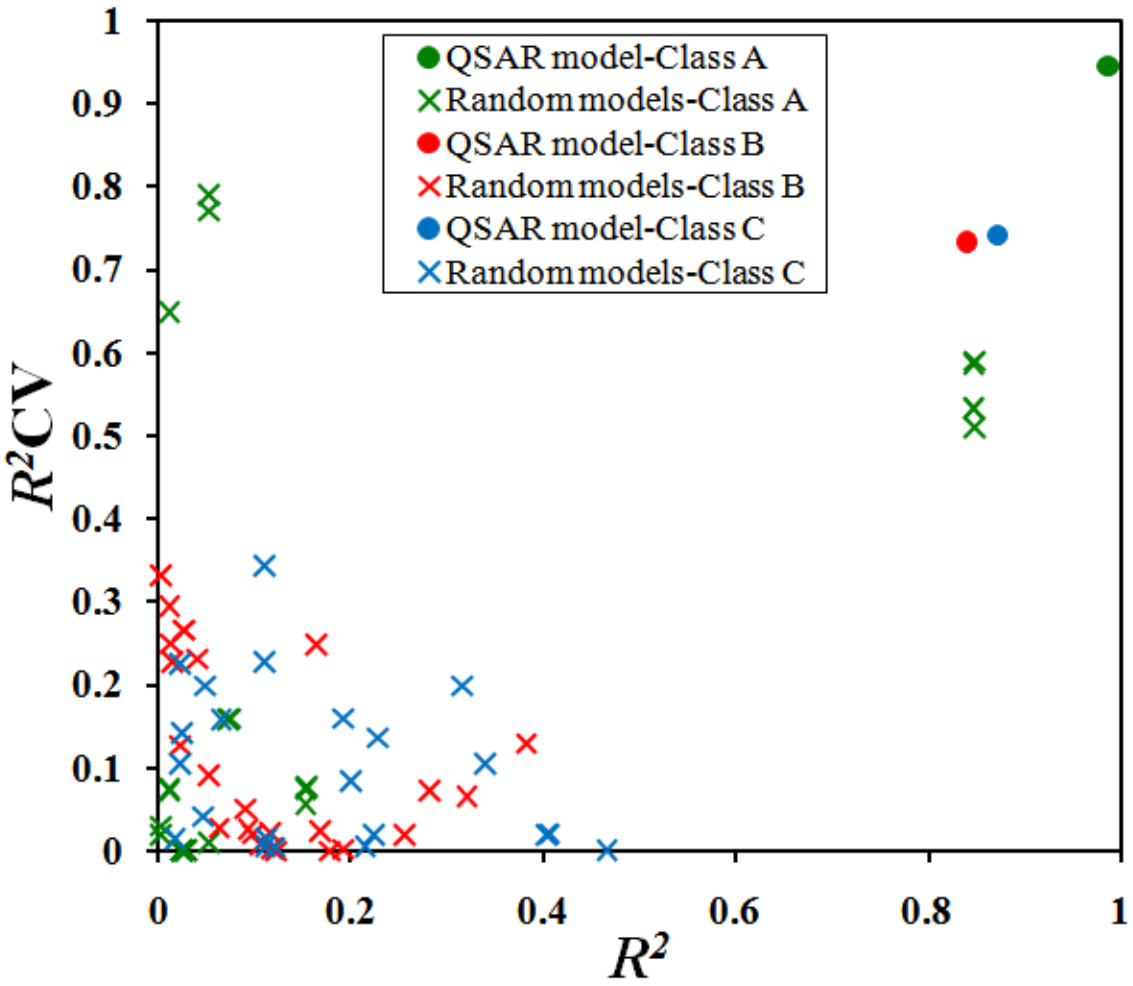

Fig. S3. The results of the Y-randomization test. The green, red, and blue circles represent for the metals or metalloids of Class A, Class B, and Class C from the QSAR models, respectively. The green, red, and blue forks represent for the metals or metalloids of Class A, Class B, and Class C from the random models, respectively.

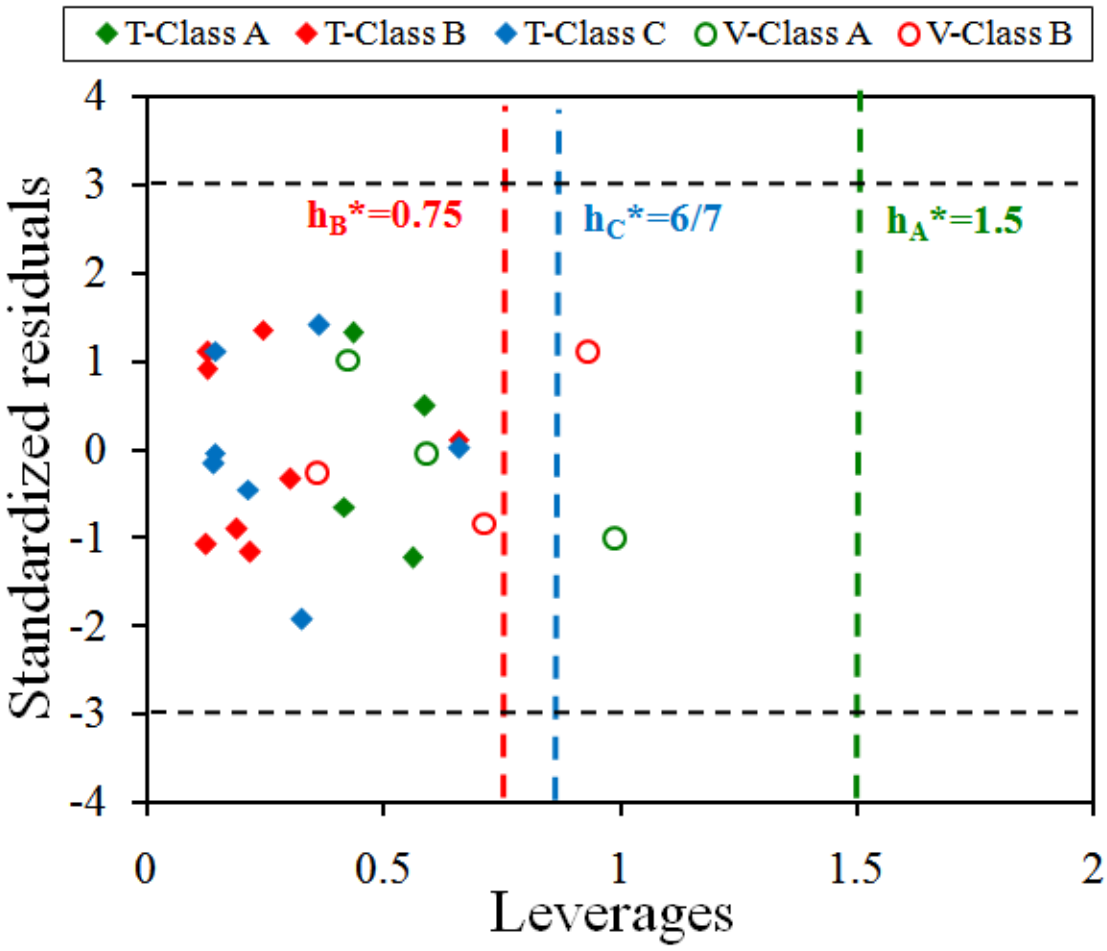

Fig. S4. The Williams plot. The green, red, and blue rhombuses represent leverage values for the metals or metalloids from the training set Class A, Class B, and Class C, respectively; the green, red, and blue circles represent leverage values for the metals or metalloids from the validation set Class A, Class B, and Class C, respectively. The green, red, and blue dotted lines represent h_A^*, h_B^*, and h_C^*, which indicates the optimum prediction space of the predicted ED values for Class A, Class B, and Class C, respectively. The black dotted lines represent plus and minus triple standardized residuals.