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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