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REVIEW

Relationships between absorption efficiency of elements in mammals and chemical properties

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Abstract

Oral absorption efficiency is an important factor to consider in human risk assessment and varies widely between elements. Linking absorption efficiency to chemical properties facilitates the understanding of underlying processes and enables extrapolation across elements. In our study, oral absorption efficiency in humans was predicted for a number of elements based on their ionization energy and electronegativity. Data on oral absorption efficiency in humans were retrieved via a literature survey. A model was developed based on the assumption that ionic species readily react with biotic ligands. Accordingly, ionization energy was presumed to represent the reactivity and absorption of atoms in the gastrointestinal tract. The coefficients of the model were parameterized by fitting the quantitative relationship between absorption efficiency and ionization energy to data collected from well-standardized studies. Generally, absorption efficiency was strongly related to ionization energy, explaining 94% of the variability in absorption efficiency between elements reported by the International Commission on Radiological Protection (ICRP). In addition, the absorption efficiencies predicted based on ionization energy were within a factor of two of those given by the ICRP ($ME = -0.05$; $RMSE = 0.31$). However, the model is not applicable to alkaline metals and molybdenum because of the uniquely high solubility of their compounds or the flexible electron configuration of these elements. Approximately 56% of the variability in absorption efficiency between elements could be explained by electronegativity. These strong relationships between absorption efficiency and ionization energy and, to a lesser extent, electronegativity indicate potential for extrapolation across elements using atomic properties.

Keywords

Absorption, mammals, metals, modeling, non-metals, oral exposure

History

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Table of Contents

Introduction

The excessive contamination of foods such as the edible parts of vegetables and fish with elements, especially metals, poses considerable risks to human health (ATSDR, 1994, 1998, 1999, 2000a,b; McLaughlin et al., 1999; US EPA, 2005). For a number of metals, dietary exposure has been reported to contribute substantially to accumulation in humans (Castro-González & Méndez-Armenta, 2008; Grasmück & Scholz, 2005; Hashmi et al., 2007; Hough et al., 2004; Lacatusu et al., 1996; Leblanc et al., 2005; MAFF, 2009; Staessen et al., 1992; Swartjes et al., 2007; Tripathi et al., 1997). For example, an estimated 40–85% of total cadmium (Cd) intake is derived from the consumption of rice, wheat, vegetables, and molluscs (WHO, 2006). Therefore, accurate estimation of chemical accumulation in humans via oral exposure is important in human risk assessment.

Because of the importance of uptake from food, as mentioned above, human exposure via this route has been restricted. For example, food quality criteria regarding maximum contaminant levels have been established (EC, 2004). Currently, exposure assessment is mainly based on a

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comparison between total daily intake and tolerable daily intake (TDI) (US EPA, 1997; Swartjes et al., 2007). The TDI is considered the reference dose, i.e. maximum permissible risk (MPR) for intake. Together with exposure conditions, the reference dose is used in the derivation of the critical soil concentration. In current approaches for risk assessment, MPR is usually derived from toxicological data using uncertainty factors (IGHRC, 2003). The uncertainty factors are applied to cover interspecies (animal to human) and intraspecies (in the human population) differences in susceptibility. However, the lack of mechanistic bases in this method may lead to substantial over- or underestimation of risks, especially when the available toxicological data are limited. More importantly, intake does not necessarily reflect the amount of elements actually accumulated in organisms. Intake represents the amount of chemicals contained in the carrier medium entering the body; however, chemicals may be absorbed at different rates from the carrier medium across the gut membrane (US EPA, 1992). Variability of three orders of magnitude in the absorption efficiency between different elements has been reported (ICRP, 2006). Consequently, intake alone is not a reliable indicator of accumulation in the body. The accumulation of chemicals in organisms is determined by the balance between uptake and elimination via different pathways. Therefore, mechanistic models that take into account fluxes via these pathways provide more reliable estimates of chemical accumulation (Le et al., 2011; Veltman et al., 2008). Data on absorption efficiency are required to simulate the kinetics of chemical uptake from oral exposure in such models.

Significant uncertainties are associated with assessments using empirical data on absorption efficiency within and between elements (US EPA, 1992, 2004). In aquatic organisms, the absorption efficiency for metals was demonstrated to depend on the covalent index, allowing for extrapolation across elements (Veltman et al., 2008). However, a similar approach has not been developed for humans. To understand the variability in absorption efficiency and to extrapolate across elements, we hypothesize that absorption efficiency can be linked to chemical properties for mammals, including humans. Our study, therefore, aimed to derive quantitative relationships between oral absorption efficiency in humans and the chemical properties of elements. Furthermore, the potential application of these chemical properties in estimating absorption efficiency in other species was also considered.

Methods

Data collection and selection

The oral absorption efficiency of elements in humans has been assessed in a number of studies, mainly based on experimental data for both humans and other mammals, particularly mice and rats. The reported absorption efficiencies vary widely. For example, the absorption efficiency for plutonium (Pu) was measured to differ by three orders of magnitude in animals (Bulman et al., 1993; Cooper & Harrison, 1982, 1984; Harrison, 1991; Harrison et al., 1981, 1986; Stather et al., 1979; Sullivan et al., 1985). To reduce the variability, we used absorption efficiencies determined by the same expert group, namely, the International Commission on Radiological Protection (ICRP) (Table 1; ICRP, 1989, 1993, 1995, 2006). The assessment of the ICRP was based on the assumption that absorption mainly occurs in the small intestine. The absorption efficiency for different age groups given by the ICRP was based on kinetic data and dosimetric models. When relevant kinetic data were not available for humans, expert adjustment was performed based on animal experiments. Together with the efficiencies determined by the ICRP, the variability in the absorption efficiencies reported in different studies is presented in Table S1, Supplementary Material.

Experimental data on humans and other mammals indicate more complete absorption for a number of elements in infants than in adults, which is attributed to various factors such as milk diet and pinocytotic activity (Barton, 1987; Brambell, 1970; Clarke & Hardy, 1971; Fritsch et al., 1988; Harrison et al., 1987; ICRP, 2006: Table 1; Sullivan, 1980a,b). The effects of age and other factors were taken into account by the ICRP in the determination of absorption efficiency in infants when empirical data were not available (ICRP, 1989, 1993, 1995, 2006). When information regarding the effects of age on the absorption efficiency in humans and other animals was lacking, kinetic data for infants and children were derived from measurements on adult humans. Because of the potential uncertainties associated with this method, the absorption efficiency in infants was not included in any further assessment in our study.

Powell et al. (1999) noted a different trend in the absorption of alkaline metals in the gastrointestinal tract compared with that of other elements and therefore classified alkaline metals as a separate group. Consequently, alkaline metals, such as calcium (Ca), strontium (Sr), cesium (Cs), barium (Ba) and radium (Ra), were not included in our model. Due to the high flexibility of its outermost electrons (Table 1), molybdenum (Mo) may exist in a number of different chemical species. This unique property corresponds to a combination of low ionization energy and high electronegativity, distinguishing Mo from other elements (Table 1). Because of this property, the bioavailability of Mo may vary widely, depending on the chemical form of intake and food properties. Molybdenum was, therefore, excluded from our study.

Model development

The uptake of elements depends on their availability for absorption by the gastrointestinal tract (Gueguen & Pointillart, 2000). In the environment, the mobility and bioavailability of substances depend on their reactions with different ligands, e.g. clay, minerals, or humic substances in soil. Mobility is determined by the proportion of reactive chemical species, e.g. free ions for metals. The fraction of these species can be obtained by using speciation models such as the Windermere Humic Aqueous Model (WHAM) or the MINTEQ model (Gustafsson, 2001, 2009; Tipping, 1994, 1998; Tipping et al., 2011). Similarly, the availability of elements for absorption in the gastrointestinal tract depends on their reactions with biotic ligands, which can also be expressed as normal chemical reactions (Di Toro et al., 2001). Because many ions are readily adsorbed onto biotic ligands in

Table 1. Absorption efficiencies in adults and infants for different elements collected from publications by the ICRP (1989, 1993, 1995, 2006) and chemical properties of the elements, i.e. ionization energy and negativity (χ_m).

		Absorption efficiency		Chemical properties		
Group	Element	Adult	Infant	Ionization energy (kJ/mol)	χ_m	Electron configuration
1	H	1	1	1312	2.2	$1s^1$
	C	1	1	1086.5	2.55	$2s^2\ 2p^2$
	Cs	1	1	375.7	0.79	$5p^6\ 6s^1$
	S	1	1	999.6	2.58	$3s^2\ 3p^4$
	Mo	1	1	684.3	2.16	$5s^1\ 4d^5$
	I	1	1	1008.4	2.66	$5s^2\ 4d^{10}\ 5p^5$
2	Se	0.8	1	941	2.55	$4s^2\ 3d^{10}\ 4p^4$
3	Zn	0.5	1	906.4	1.65	$4s^2\ 3d^{10}$
	Tc	0.5	1	702	1.9	$5s^2\ 4d^5$
	Po	0.5	1	812.1	2.0	$5d^{10}\ 6p^4$
4	Te	0.3	0.6	869.3	2.1	$5s^2\ 5p^4$
	Sr	0.3	0.6	549.5	0.95	$4p^6\ 5s^2$
	Ca	0.3	0.6	589.8	1	$3p^6\ 4s^2$
5	Ba	0.2	0.6	502.9	0.89	$5p^6\ 6s^2$
	Ra	0.2	0.6	509.3	0.9	$6s^2\ 4f^{14}\ 5d^{10}\ 7s^2$
	Pb	0.2	0.6	715.6	2.33	$5d^{10}\ 6s^2\ 6p^2$
6	Co	0.1	0.6	760.4	1.88	$4s^2\ 3d^7$
	Fe	0.1	0.6	762.5	1.83	$4s^2\ 3d^6$
	Sb	0.1	0.2	834	2.05	$4d^{10}\ 5p^3$
7	Ru	0.05	0.1	710.2	2.2	$5s^1\ 4d^7$
	Ni	0.05	0.1	737.1	1.91	$4s^2\ 3d^8/4s^1\ 3d^9$
	Ag	0.05	0.1	731	1.93	$5s^1\ 4d^{10}$
8	U	0.02	0.04	597.6	1.38	$7s^2\ 5f^3\ 6d^1$
9	Zr	0.01	0.04	640.1	1.33	$5s^2\ 4d^2$
	Nb	0.01	0.02	652.1	1.6	$5s^1\ 4d^4$
	Ce	0.01	0.02	534.4	1.2	$6s^2\ 4f^1\ 5d^1$
10	Th	0.0005	0.005	587	1.3	$7s^2\ 6d^2$
	Np	0.0005	0.005	604.5	1.36	$7s^2\ 5f^4\ 6d^1$
	Pu	0.0005	0.005	584.7	1.28	$7s^2\ 5f^6$
	Am	0.0005	0.005	584.7	1.3	$7s^2\ 5f^7$

the gut and do not easily cross membranes, the uptake of elements into the body would be expected to decrease with their tendency to be ionized. Accordingly, the absorption efficiency p is expected to be inversely proportional to the rate of electron dissociation to form cations k, i.e. $p \sim k^{-1}$. This function is similar to the relationship of reactivity with electron configuration and ionization reported by Hartung & Adkins (1927). The rate of electron dissociation k (s^{-1}) is, in turn, an exponential function of the activation or ionization energy (Gross, 2011; Lias & Bartmess, 2000):

$$k = c \cdot e^{-n \cdot I} \qquad (1)$$

where I (kJ/mol) is the ionization energy and n (mol) represents the amount of electrons dissociated.

Moreover, the rate of electron dissociation is limited by internal energy (Gross, 2011). When the ionization energy exceeds the internal energy, no electrons are dissociated and the element is completely absorbed, i.e. $p \to 1$ ($p_{\max}$). This limitation can be integrated in modeling absorption efficiency as follows:

$$p = \frac{p_{\max} \cdot a \cdot e^{n \cdot I}}{E_m + a \cdot e^{n \cdot I}} = \frac{a \cdot e^{n \cdot I}}{E_m + a \cdot e^{n \cdot I}} \qquad (2)$$

where $p_{\max}$ is the maximum absorption efficiency and equals 1 and E_m (kJ) represents the energy level at which the absorption efficiency equals half of the maximum efficiency, i.e. 50% of the oral dose is absorbed from the gastrointestinal tract. So, E_m (kJ) can be derived from the ionization energy at an absorption efficiency of 0.5, I_m (kJ/mol):

$$E_m = \frac{I_m}{N_A} \qquad (3)$$

where N_A (mol^{-1}) is Avogadro's number $N_A = 6.022 \times 10^{23}$. Consequently, absorption efficiency can be expressed as a function of ionization energy according to Equation (4):

$$p = \frac{a \times e^{n \times I}}{\frac{I_m}{N_A} + a \times e^{n \times I}} \qquad (4)$$

I_m (mol^{-1}) and the coefficients a (dimensionless) and n (mol) in Equation (4) were determined by fitting the equation to the data collected.

The foregoing description provides a partial mechanistic understanding of the relationship between absorption efficiency and ionization energy. Simplification of the model by a regression relationship between absorption efficiency and a dimensionless chemical property may facilitate further extrapolation. This simplification is further motivated when oral exposure is combined with other uptake routes in predicting total accumulation. Several chemical properties that reflect the affinity of elements for attracting electrons or the tendency to dissociate electrons was considered by van Kolck et al. (2008) in modeling metal bioaccumulation. Among these chemical characteristics, only dimensionless electronegativity (χ_m; Pauling scale) represents the chemistry of atoms, whereas others describe the chemical characteristics of metal cations. Therefore, the potential use of electronegativity as a predictor of absorption efficiency was also examined. A best-fit curve between the absorption efficiencies collected and the electronegativity introduced by Pauling (1932) was derived.

Model assessment

The model developed based on data provided by the ICRP was assessed by using another data set on absorption efficiency in humans reported by Owen (1990). As mentioned above, data for animals, including ruminants, were also used in the assessment by the ICRP. Therefore, the data set provided by Howard et al. (2009) for ruminants was also used to assess the predictive potential of our model for humans. However, our assessment of the predictive potential of the model using data set given by Howard et al. (2009) did not actually validate the model because data on ruminants were considered in the determination of absorption efficiency both by Howard et al. (2009) and the ICRP.

Statistical analyses

The potential of our model for predicting absorption efficiency was evaluated by means of different statistical parameters. The capacity of the model for explaining the variability in absorption efficiency across elements was assessed in terms of the coefficient of determination (r^2). The performance of the model was additionally evaluated by two other statistical parameters, namely, the normalized mean error (ME) and the normalized root mean square error (RMSE). The mean error indicates whether the absorption efficiency is over- (ME$>$0) or underestimated (ME$<$0). The lower the value of the RMSE is, the more accurate the model is.

Results

Relationships between absorption efficiency and ionization energy in humans

In general, absorption efficiency increased with increasing ionization energy as expected by our model (Figure 1A). Approximately 94% of the variability in the absorption efficiency between elements obtained from the ICRP publications was explained by ionization energy according to Equation (4) ($r^2 = 0.94$; $p < 0.00001$; Figure 1A). The absorption efficiency could be predicted well by the model (ME $= -0.05$; RMSE $= 0.31$; Table 2). Estimated efficiencies were within a factor of two of the values reported in the ICRP publications (Table 2). The model also performed well in the assessments using other data sets, although larger deviations between the predictions and the measurements were observed (Table 2). In the assessment based on the review of Owen (1990), absorption efficiency was overestimated, but the predictions were within a factor of two of the measurements (ME $= 0.27$; RMSE $= 0.81$; Table 2). Additionally, the predictions generated by our model were significantly correlated with the values reported by Howard et al. (2009) for ruminants, indicating that ionization energy is a potential predictor of absorption efficiency in ruminants ($p < 0.05$; Figure 1B). Larger deviations between the predictions obtained by using the model for humans and the measurements for ruminants imply that the absorption efficiencies in ruminants were generally lower than those in humans (ME $= 0.92$; RMSE $= 1.22$; Table 2).

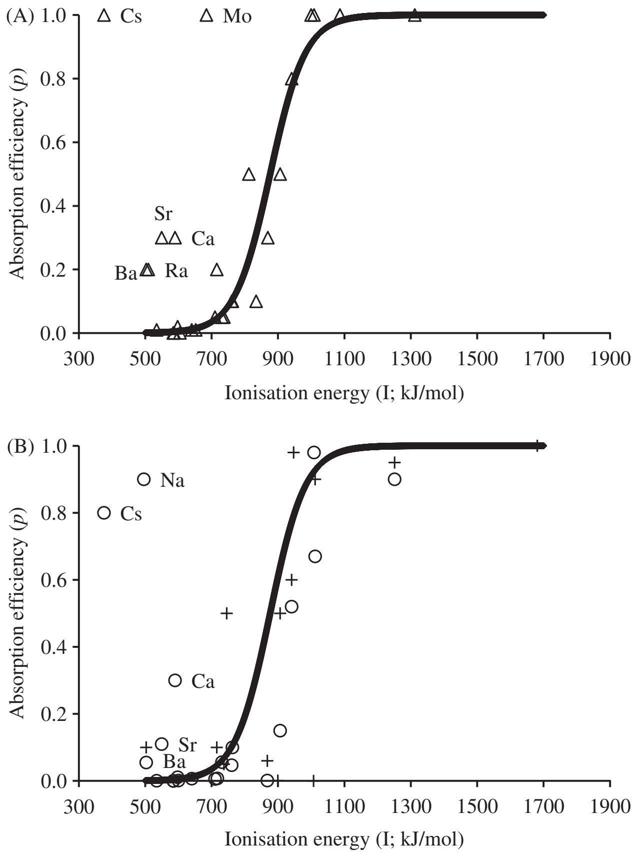

Figure 1. Comparison between the absorption efficiencies predicted based on ionization energy according to Equation 4 ($I_m = 859.25$ kJ/mol; $a = 6 \cdot 10^{-29}$; $K = 1.92 \cdot 10^{-2}$), denoted by the solid lines, and the absorption efficiencies: (A) reported in ICRP publications (ICRP, 1989, 1993, 1995, 2006) for humans (denoted by the triangles); and (B) reported in the study of Owen (1990) for humans (denoted by the plus symbols) and the study of Howard et al. (2009) for ruminants (denoted by the circles).

Relationship between absorption efficiency and electronegativity

Approximately 56% of the variability in the absorption efficiency between elements reported in the ICRP publications could be explained by a quadratic regression with respect to electronegativity (Figure 2A). Generally, the absorption efficiencies predicted by using the regression were within a factor of two of the efficiencies reported in the ICRP publications (ICRP, 1989, 1993, 1995, 2006) and in Owen (1990). However, the estimations based on electronegativity deviated more from the measurements compared with those based on ionization energy (Table 2). Moreover, the predictions based on electronegativity were significantly correlated with

Table 2. Performance of the model based on ionization energy and the regression based on electronegativity in estimating absorption efficiency expressed by the normalized mean error (ME) and the normalized root mean square error (RMSE).

		Studies		
Descriptors	Statistic parameters	ICRP (1989, 1993, 1995, 2006)	Owen (1990)	Howard et al. (2009)
Ionization energy	ME	−0.05	0.27	0.92
	RMSE	0.31	0.81	1.22
Electronegativity	ME	−0.33	0.86	9.61
	RMSE	0.71	0.49	1.41

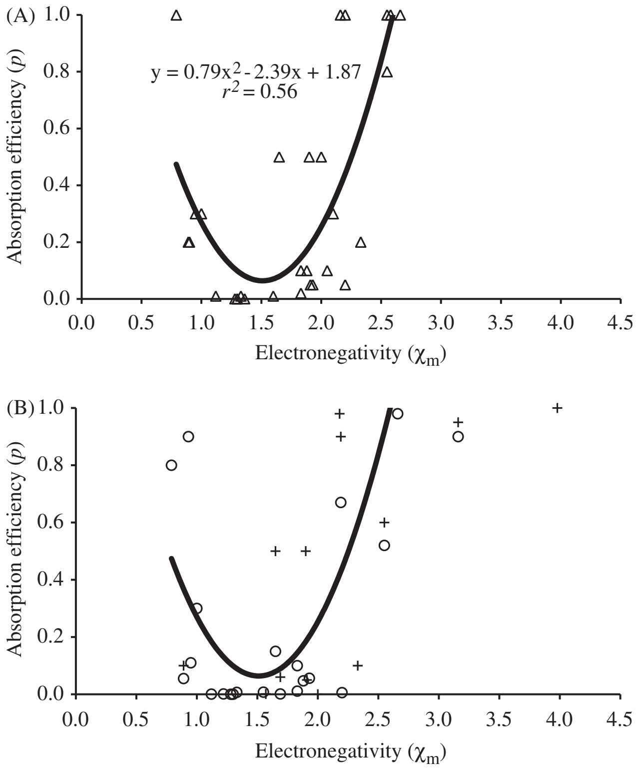

Figure 2. Relationship between absorption efficiency and electronegativity. The solid line represents the best-fit curve describing the relationship between absorption efficiency and electronegativity using data reported in ICRP publications (ICRP, 1989, 1993, 1995, 2006). The triangles (A) and the plus symbols (B) represent the absorption efficiencies for humans reported in ICRP publications and Owen (1990), respectively. The circles (B) represent the absorption efficiencies for ruminants reported in the review of Howard et al. (2009).

the measurements presented by Owen (1990) and Howard et al. (2009) ($p < 0.05$; Figure 2B). However, the relationship based on electronegativity overestimated the absorption efficiencies compared with the data reported by Owen (1990) (ME = 0.86; NRMSE = 0.49). Lower absorption efficiencies in ruminants, as reported by Howard et al. (2009), compared with the efficiencies in humans were also observed here (Table 2).

Comparison of absorption efficiency in humans and other species

A strongly positive relationship was observed between absorption efficiencies in humans and those in mussels and fish, as shown in Figure S1, Supplementary Material.

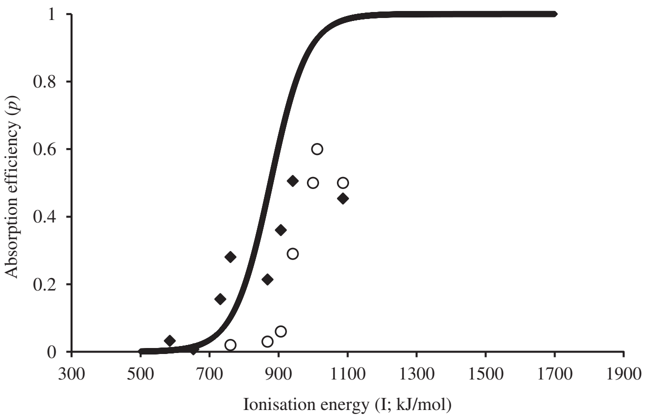

Figure 3. Comparison of the absorption efficiencies predicted by the model for humans and the absorption efficiencies measured for mussels (Wang & Fisher, 1996) and fish (Reinfelder & Fisher, 1994b): the solid line represents the predictions based on the relationship with ionization energy (Equation 4), and the squares and circles represent the measurements obtained for mussels and fish, respectively.

However, substantial deviations were observed in the measurements of absorption efficiency for these aquatic species from the predictions based on the relationship established for humans (Figure 3). Absorption efficiencies in adult humans were weakly related to those in oysters and clams measured by Reinfelder and Fisher (1994a,b) (Figure S1, Supplementary Material).

Discussion

Sources of uncertainties

Generally, there are significant uncertainties in estimating absorption efficiency of elements using current approaches (Diamond et al., 1997). In our study, only uncertainties resulting from the consideration of chemical-specific properties were considered. Exposure conditions that were not considered in our study may have significant influence on the absorption efficiency (US EPA, 1992).

The absorption efficiency of elements is affected by a number of factors, including age, chemical forms of intake, dose and route of exposure, environmental matrix, diet composition, nutritional status, intestinal content, and interactions between different substances (Bhattacharyya et al., 2000; Diamond et al., 1998; ICRP, 2006; Kello et al., 1979; WHO, 2006). For example, a difference of one order of magnitude in the absorption efficiency of lead (Pb) was attributed to a variety of factors, including the status of iron (Fe) or zinc (Zn) in the body, the content of other elements, e.g. Ca, phosphorus (P), fat, vitamin D and protein in the intestine, the physical and chemical forms of intake and fasting time (Anders et al., 1982; Conrad & Barton, 1978; Heard & Chamberlain, 1982; Holt et al., 1987; Jugo & Kello, 1975; Mahaffey, 1980; Mallon, 1983; Miller et al., 1990; Morton et al., 1985). Both the chemical forms of the ingested elements and diet affect absorption efficiency (ICRP, 2006). For instance, the valency state was observed to affect the hydrolysis and transport of neptunium (Np) and Pu to blood, thus influencing the resulting absorption efficiency (Harrison et al., 1984; Metivier et al., 1983, 1985; Sullivan et al., 1983a,b). A number of elements, e.g. Pu, Cd, Pb, and aluminum (Al), have been reported to be absorbed in higher quantities when they were incorporated in complexing agents such as citrates, phytates, and other organic acids than when they occur in their inorganic forms, e.g. nitrate, chloride, silicate, and phosphate (Bercovitz & Laufer, 1991; Cooper & Harrison, 1982, 1984; Day et al., 1991; Drueke, 2002; Drueke et al., 1997; Flanagan et al., 1978; Friberg et al., 1974; Jouhanneau et al., 1997; Kaehny et al., 1977; Priest et al., 1996; Reilly, 1980). Moreover, additions of algae, milk or orange juice have been shown to increase absorption efficiency in humans (Garcia-Casal et al., 2009; Sullivan et al., 1983a,b). In the ICRP assessment, data were obtained under different exposure conditions, and in particular, different chemical forms of intake and food types, leading to difficulties in quantitatively investigating the effects of these factors. Further studies must be conducted individually for single elements whose absorption efficiency has been determined in different sets with only one varying factor, e.g. chemical forms of intake, while keeping other exposure conditions constant to derive quantitative relationships between absorption efficiency and these factors. The absorption efficiency of elements, especially metals, is further influenced by their interactions with other elements (Bannon et al., 2002; Bogden et al., 1992; Elsenhans et al., 2011; Rossander-Hulten et al., 1991; Sandstrom et al., 1985; Solomons & Jacob, 1981). Interactions may occur between elements with similar physicochemical properties, absorption pathways, or transport proteins (Bridges & Zalups, 2005; Cannata et al., 1991; Fernandez-Menendez et al., 1991; Goyer, 1997; Rossander-Hulten et al., 1991; Simons, 1986). In addition, absorption efficiency is affected by the specific physiological demands of organisms, e.g. those experienced during pregnancy and lactation in female adults or increased growth in children (Allen, 1982; Cross et al., 1995). The absorption of elements, especially metals, is also affected by the production of metallothionein (Andersen et al., 1992; Min et al., 1991).

Chemical properties determine absorption efficiency of elements

The good performance of the model based on ionization energy demonstrates that ionization energy is a potential unifying factor in modeling absorption efficiency in humans. This modeling approach is further supported by the relationship between the specific absorbed fraction and the energy of electrons, as reported by the ICRP (2006). Similar to our research, several previous studies show that chemical properties indicating affinity for electrons might be used as descriptors of metal bioaccumulation (Le et al., 2011; van Kolck et al., 2008; Veltman et al., 2008). However, a mechanistic understanding of the relationship between bioaccumulation and these chemical properties is lacking in these studies. Our research provides preliminary insights into this issue. In particular, properties such as covalent index and electronegativity, which reflect affinity for electrons, are related to ionization energy. Ionization energy, in turn, determines the reactivity and eventual absorption of atoms in the gastrointestinal tract. Although a mechanistic explanation for the U-shaped relationship between absorption efficiency and electronegativity is lacking, our theory, which focuses on the relationship between absorption and reactivity, may contribute to the understanding of this behavior. Characteristics of electron configuration may determine the reactivity of atoms, thus accounting for the U-shaped relationship observed. Most of the elements in the intermediate range of electronegativity are d- or f-block elements (Table 1). Electrons in d and f orbitals are highly active, contributing to the high reactivity of these elements and low absorption efficiency. In contrast, elements with high or low electronegativity are mainly s- or p-block elements, which have more stable ions at the outermost electron layer. Consequently, these elements may exhibit low reactivity, which accounts for their high absorption efficiency. Moreover, our study shows that electronegativity has a lower potential than ionization energy for explaining the variability in absorption efficiency between elements. Therefore, regressions of absorption efficiency on electronegativity or covalent index developed and applied in previous studies may be further improved by taking into account other factors. This possibility is supported by the considerable potential of properties such as molecular weight for explaining the variations in metal accumulation in mussels, as reported by Hendriks et al. (1998).

Some chemical properties are not completely captured for by the value of the first ionization energy, accounting for the exceptions of alkaline metals and Mo as mentioned in the *Methods* section. A different pattern of absorption efficiency for alkaline metals, as reported by Powell et al. (1999), was also observed in the publications of the ICRP (ICRP, 1989, 1993, 1995, 2006) and in the study of Howard et al. (2009) (Figure 1A and B). The exception for alkaline metals is attributed to the high solubility of their compounds, which influences their bioavailability (Hansen et al., 1998). In general, the solubility of salts increases with the increasing ionization energy of the corresponding metals. However, this trend is not observed for alkaline metals. Despite their low ionization energy, the high solubility of their compounds might contribute to the high bioavailability of alkaline metals, thus accounting for the high absorption efficiency. Because this chemical property is not captured by ionization energy, the absorption efficiency of alkaline metals could not be adequately modeled based on ionization energy alone. Similarly, characteristics of electron configuration are not completely captured by ionization energy. Therefore, chemical forms of intake and diet composition should be considered together with chemical properties to obtain reliable estimates of absorption efficiency for elements such as Mo.

Estimations of oral absorption efficiency allow for the prediction of chemical accumulation in humans. In particular, accumulation from food can be estimated by considering intake, which is a function of the concentration of elements in food and the amount of food consumed, and absorption efficiency, as successfully achieved for other organisms (Le et al., 2011). The reliability of estimates of internal concentration (or body burden) in humans may be further improved by integrating the predicted oral uptake into physiologically based toxicokinetic (PBTK) models, taking into account other routes of uptake (Jongeneelen & Ten

Berge, 2011). Accordingly, potential risks to humans can be assessed by comparing the predicted internal concentration with a critical internal concentration, which is derived from normal dose-response curves. This comparison is a better indicator of the risks posed to humans compared with the ratio between the total daily intake and TDI commonly used in current risk assessment frameworks.

Species-specific absorption efficiency

The statistically significant correlation between absorption efficiencies in humans and in mussels and fish indicates that the chemical properties of elements, with respect to human and ruminant absorption, might also help explain the variability in absorption efficiency in mussels and fish. Large deviations between the absorption efficiencies predicted by using the relationship established for humans and the efficiencies measured in mussels and fish can be attributed to the distinct absorbability of elements across different species. This species-specific absorbability is, in turn, derived from differences in toxicokinetics and toxicodynamics. In particular, differences in the contribution of various uptake routes between species may lead to variations in absorption efficiency. For instance, the dominance of uptake from water, as observed for a number of elements in mussels and fish by Le et al. (2011) and Luoma & Rainbow (2005), may be related to lower absorption efficiencies in these species compared with those in humans, as mentioned above. Variations in absorption efficiency across species are additionally caused by differences in toxicodynamic processes. For example, the availability of chemicals for absorption depends on the pH conditions in the gastrointestinal tract (Bucking & Wood, 2009). Thus, pH affects the release of elements from the carrier medium. Furthermore, the effects of the competition with H^+ for binding sites on biotic ligands, e.g. gills in fish, might affect the availability of substances (Di Toro et al., 2001; Le et al., 2012). Decreases in pH might reduce the binding of elements to biotic ligands, thus increasing the availability of these chemicals and their absorption efficiency. This explanation may account for the difference in absorption efficiency between humans and aquatic species observed in our study. In particular, higher absorption efficiencies in humans than in fish, as shown in Figure 3, may be attributed to the slightly more acidic environment in the human digestive system (pH: 5–7.4; Fallingborg, 1999) compared with the relatively alkaline environment in the fish intestine (pH: 7.5–8.6; Sugiura et al., 2006; Taylor & Grosell, 2006). Another factor that might contribute to species-specific absorbability is the variation in the diet compositions of different species, which has been reported to affect absorption efficiency, as presented above.

As mentioned in the *Introduction* section, there are substantial uncertainties involved in determining MPR by using uncertainty factors in current human risk assessment frameworks. The uncertainties that arise in using this method may be reduced by integrating accumulation mechanisms such as those proposed in our approach. Moreover, the findings of our study that the theory applied to humans is potentially applicable to other species offer the opportunity to develop a mechanistic method for estimating the absorption efficiency of different species. The development of such a method should further reduce the uncertainties associated with the use of animal-to-human uncertainty factors.

In summary, absorption efficiency can be related to ionization energy for many elements. However, some chemical properties of elements, such as the solubility of their compounds and characteristics of electron configuration, are not entirely captured by ionization energy. In addition, absorption efficiency is influenced by exposure conditions, especially the chemical form of intake, diet composition, and the importance of other routes of intake. The exclusion of these factors is a potential source of uncertainty in modeling absorption efficiency.

Declaration of interest

The authors' affiliation is as shown on the cover page. The authors have sole responsibility for the writing and content of the paper.

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