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Review

Competition between Cd(II) and other divalent transition metal ions during complex formation with amino acids, peptides, and chelating agents

Maurizio Remelli[a, *]
rmm@unife.it

Valeria M. Nurchi[b, *]
nurchi@unica.it

Joanna I. Lachowicz[b]

Serenella Medici[c]

M. Antonietta Zoroddu[c]

Massimiliano Peana[c]

[a]Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via Fossato di Mortara 7, I-44121 Ferrara, Italy

[b]Department of Chemical and Geological Sciences, University of Cagliari, Cittadella Universitaria, I-09042 Monserrato-Cagliari, Italy

[c]Department of Chemistry and Pharmacy, University of Sassari, Via Vienna 2, I-07100 Sassari, Italy

*Corresponding authors.

Abstract

Cadmium is not an essential element for humans, but instead its compounds are known for their toxicity. In addition to the risks for workers in industries that use cadmium, this metal can enter the food chain at different levels to be absorbed by the body, where it replaces other metals with similar chemical activity. This also applies to the cadmium inhaled via cigarette smoking. Thus, understanding the interactions between cadmium and biologically relevant molecules, such as amino acids, peptides, and proteins, is important, but it is also useful to study the chelating methods that can cure or alleviate acute or chronic cadmium poisoning cases. $^{111/113}$Cd isotopes are used as NMR probes to determine the complex formation sites and geometry of metals in metalloproteins and metalloenzymes. This review provides a general introduction to the general properties of cadmium as well as the main uses of this metal, its compounds, and artifacts. The toxicity of cadmium in humans is also discussed and the most significant results regarding the interactions between cadmium and other potentially competing divalent metal ions with biological relevance, i.e. Fe(II), Zn(II), Mn(II), Ni(II), and Cu(II), and amino acids and peptides, particularly those containing histidine and/or thiolic groups, are collected. To the best of our knowledge, this is the most comprehensive summary reported for the speciation models of these systems. Distribution and competition diagrams were constructed to facilitate comparisons of the binding abilities of different metals with the same ligand (or vice versa) over a wide pH range and with different reagent concentrations and/or concentration ratios, thereby providing insights into the in vivo behavior both inside and outside cells where the pH and concentration can be very different. The vast topic of complexes with phytochelatins and metallothioneins is left for a more focused study. Finally, cadmium chelators with potential pharmacological applications are thoroughly reviewed.

Keywords: Amino acid; Cadmium toxicity; Chelating agent; Complex formation equilibria; Peptide; Protein

1 Introduction

In an interesting article, Mary E. Weeks (1932) [1] described how Friedrich Stromeyer, a German chemist who worked as an inspector of apothecaries, serendipitously discovered cadmium: "*In the year 1817 a number of preparations of zinc oxide sold by German apothecaries were confiscated by the inspectors, who found that zinc carbonate had been substituted for the oxide, that the carbonate became yellow upon heating, and that, when hydrogen sulfide was passed into an acid solution of the carbonate, a yellow precipitate resembling arsenious sulfide was thrown down. The researches of Dr. Stromeyer, Dr. Roloff, and Mr. Hermann proved, however, that this yellow precipitate was not arsenic sulfide, but the sulfide of an unknown metal. Thus the good name of the manufacturing pharmacies was restored, and the chemical world was enriched by the discovery of the new element, cadmium.*" The name cadmium derives from the Latin word for zinc carbonate ores, *cadmia*.

Since its discovery, this element and its compounds have found an increasing number of applications due to their peculiar characteristics. However, the extremely high toxicity of cadmium, which is classified as one of the most dangerous compounds for human health, has become increasingly evident over time. International regulations have restricted the use of cadmium, but its toxic effects, including those in the form of nanoparticles [2], still comprise a major health concern throughout the world. Thus, the present review provides a comprehensive examination of this subject, including the poisonous effects of cadmium, its behavior in the human body, its ability to form complexes with amino acids and peptides, and recent developments in cadmium chelation therapy. Moreover, this review compares speciation models for the formation of complexes of Cd(II) or potentially competing divalent metal ions with biological relevance (Fe(II), Zn(II), Mn(II), Ni(II), and Cu(II)), with amino acids and peptides. In addition, distribution diagrams are reported and competition plots are drawn for the first time, which facilitate direct comparisons of the binding abilities of different metals with the same ligand. In fact, the competition between cadmium and other metals in vivo is one of the main reasons for the toxicity of cadmium. Different issues are considered such as the main applications of cadmium in order to elucidate the connections between the occurrence of poisoning and the mechanisms responsible for the interactions with the main biomolecules in living organisms.

1.1 General properties of cadmium

First, the general properties of cadmium are summarized, including its complex formation behavior, to understand the types of ligands and coordinating groups that may interact with cadmium to obtain toxic effects.

Cadmium (atomic weight 112.41 g/mol) is a silver-white metal with medium density (8.7 g/mL). Its most significant properties are high electrical conductivity, great resistance to corrosion, and a low melting point, which determine its main industrial applications.

Cadmium is classified in Group IIB in the periodic table together with zinc and mercury. It is found with 0, +1, and +2 oxidation states, but only Cd(II) compounds with the $4d^{10}$ configuration are found in normal conditions. The ionic radius of Cd(II) is 0.97 Å, which is almost equal to that of Ca(II) and Na(I) with 0.99 Å and 1.02 Å, respectively. This explains the substitution of these two ions by Cd(II) in their mineral forms, especially calcium ions in bones.

The stability of Cd(II) complexes with external ligands, or with endogenous ligands as proteins or nucleic acids, depends on the changes in free energy after complex formation, which are also related to the chemical features of the ligand (hard/soft character, *chelate effect*, and stereochemistry). According to the hard-soft classification [3] of metal ions and the principal coordinating groups, Cd(II) is a reasonably soft metal ion, which prefers coordination with soft sulfur-containing donor groups, although coordination with nitrogen and oxygen donor atoms is found frequently. The structure and denticity of the ligands determine the pre-organization of the complex [4] and the degree of favorable entropic contribution due to the chelate effect [5].

The stereochemistry of Cd(II) complexes with ligands in biological fluids is useful for understanding the biological behavior of Cd(II). Most of the information available regarding the coordination chemistry of Cd(II) is derived from solid-state X-ray structures. Details of the stereochemistry of Cd(II) coordination compounds were provided in reviews by Tuck [6] and Borsari [7,8]. Cadmium is found in a large number of complexes with coordination numbers (CN) from 2 to 8, but the most frequent structures are regular tetrahedral (CN = 4) and octahedral (CN = 6) [9].

When evaluating the interaction of cadmium with biological ligands, it is important to consider the kinetic behavior as well as thermodynamic properties. The exchange rates for coordinated water provide insights into the lability of the metal ion, which is unique for each metal ion [10]. The water-exchange rate is high for cadmium and thus an equilibrium is reached rapidly with biological ligands. This implies that kinetic factors influence the distribution of Cd(II) between different ligands in the body only to a limited extent, ~~where~~while this is affected mainly by thermodynamic parameters.

2 Uses of cadmium and cadmium compounds

The rate of cadmium consumption for various end uses has varied over the years, as shown by the data for 1995–2013 in Table 1 [11]. Cadmium is a by-product of zinc manufacture, so its total global production depends on the demand for zinc rather than cadmium. Since 1990, the world consumption of cadmium has been constant (about 20,000 tons per year) but major changes have occurred in the geographical distribution of production, where that in Asia has increased significantly since 1997, whereas that in Europe has decreased. At present, the largest producer of cadmium is China, with one-third of the global production, followed by Korea and Japan. Cadmium is highly recycled and the nine major recycling plants are located in the USA, Europe, and Japan, which can handle about 20,000 tons of NiCd batteries per year [12].

Table 1 Industrial uses of cadmium during 1995–2013 [11].

Year	Batteries	Pigments	Coatings and plating	Stabilizers for plastics	Nonferrous alloys/Other
1995	65	14	9	9	3
2004	81	10	7	1.5	0.5
2013	86	9	4	<1	<0.5

The industrialized countries have significantly reduced their usage of cadmium and limited the release of cadmium into the environment, but the consumption of cadmium has continued or increased in developing countries, such as in the production of plastics and paints. The less strict regulations in these regions have resulted in a number of health and environmental risks related to the use, management, and disposal of cadmium-containing products. Thus, a non-negligible amount of cadmium is released into the environment [13].

2.1 Pigments for artists

In the 1840s, cadmium sulfide was the first cadmium compound to be applied extensively, where artists used it as pigment in oil and watercolor paints [14], in addition to the other new, inorganic pigments produced by the nascent chemical industry. These new paints were better than the old ones in many respects, particularly in terms of their fastness, color intensity, and coverage. Famous painters such as Vincent van Gogh and Claude Monet frequently used CdS [15,16]. However, the fading of the yellow-colored CdS pigments in these paintings has been reported in recent years [17], and there has been a detailed chemical study of the chemical mechanisms that underlie this degradation process [18].

2.2 Pigments

CdS and CdS/CdSe are used in many applications as pigments, with colors ranging from yellow to red, in canvas paints but also in ceramics, glasses, plastics, and mural paintings. In addition to their coloring properties, they tolerate high temperatures, which facilitates their application in processes that require heat treatment [19]. Cadmium compounds were also used as tanning agents for leather from the second half of the 19th century until the last decade of the 20th century.

2.3 Nickel-cadmium batteries

At present, rechargeable nickel-cadmium batteries (Ni-Cd) are the main application of cadmium. In Sweden, Waldmar Jungner invented the Ni-Cd battery during 1899, which uses nickel as the cathode and cadmium as the anode [20]. Subsequently, the high cost of these materials compared with lead batteries prevented the diffusion of Ni-Cd batteries, but improvements made by Shlecht and Ackermann in 1932 (higher load currents and greater longevity), as well as by Georg Neumann in 1947 (sealing the cell), allowed Ni-Cd batteries to enter various applications [20,21]. For many years, Ni-Cd batteries were the only type of rechargeable battery used in portable power tools, as well as cellular phones, camcorders, and portable laptop computers. Indeed, Ni-Cd batteries represented the industrial standard for portable computers until 1992. Governments have recommended that consumers recycle Ni-Cd batteries because of their cadmium content, but in the 1990s, the public in Europe were made aware of the environmental harm caused by the careless disposal of Ni-Cd batteries. The European Union's (EU) Battery Directive 2006/66/EC now limits the trade of Ni-Cd batteries in Europe, except when no alternative is available [22].

2.4 Coating and solder alloys

In the middle of the 20th century, metallurgists began to use cadmium for coating metals and alloys to prevent corrosion, where this process rapidly became the most common application of cadmium. In the soldering process, a fusible alloy works as a filler material to make joints between compatible materials. Cadmium has the advantageous characteristics of both reducing the working temperature required and favorable flow properties. Thus, 16–25% cadmium is commonly present in cadmium-containing silver solder. However, the EU has banned the use of cadmium in soldering or brazing because of its toxic effects, although there are some exceptions related to safety, defense, and aerospace applications. Therefore, in 2013, the main uses of cadmium were in the aerospace and defense industries.

2.5 Cadmium stabilizers in plastic production

Manufacturers have long used cadmium salts, stearate, or laurate as PVC stabilizers because of the high heat stability and excellent weatherability that they impart to plastic compounds. PVC was used in products such as roofing membranes and window frames, but never in food utensils or toys. EU Directive 91/338 [23] allowed the use of cadmium stabilizers in window frames and roofing membranes, but the Voluntary Agreement of the PVC Industry signed in 2000 ended the use of cadmium stabilizers [24]. In 2011, regulation 494/2011 amended the requirements regarding the use of cadmium in the EU by extending the 0.01% cadmium limit to all PVC items, except for rigid PVC construction products containing recovered PVC, by the end of 2017 [25].

2.6 Television tubes

Cathode ray tubes (CRTs) in televisions and computer screens represent the main form of waste electrical equipment that needs recycling. CRTs contain a number of toxic metals such as lead, cadmium, barium, and fluorescent powders, which can be released into the environment if appropriate recycling operations are not conducted. Exposure to these dangerous compounds has been assessed in workplaces for the treatment of CRTs and recommendations were defined for reducing the chemical risks [26].

2.7 Cadmium telluride solar cells

Solar cells are a photovoltaic technology for efficiently absorbing sunlight and converting it into electricity. Cadmium telluride (CdTe) is the second most widely utilized material in solar cells after silicon. The major advantage of CdTe is its low cost [27] and CdTe appears to be less toxic than other cadmium compounds. Nevertheless, it is toxic if ingested, inhaled, or handled improperly [28]. In the USA, the need for correct disposal and the long-term safety of CdTe are known issues, and recycling the solar cell modules can resolve environmental concerns [29]. The approach to CdTe safety is much more cautious in the EU, where regulating the use of CdTe is currently being discussed [27].

2.8 Phosphate fertilizers

Phosphate fertilizers are used widely in agriculture and they can contain non-negligible amounts of cadmium (up to 0.01% according to the geological origin of phosphate [30]). This comprises a serious environmental problem because Cd(II) can be absorbed by different plants, and thus it may become a severe health risk for humans by passing through the food chain. The European Commission is considering the possibility of implementing an EU-wide charge on cadmium in fertilizers to improve the competitive position of "low-Cd" products. Several EU Member States have tried to reduce cadmium through different policy instruments, but there is no general EU rule on this issue at present.

3 Toxicity of cadmium in humans

Cadmium is not an essential element for humans and its requirement by other forms of life is limited to a single case in marine algae under zinc deficiency conditions [31]. All forms of cadmium are toxic and the International Agency for Research on Cancer has classified it as a human carcinogen [32]. The US Agency for Toxic Substances and Disease Registry [33] provides a list of the substances that can cause major human health problems due to both their toxicity and through potential human exposure (Table 2). This list is revised periodically to consider any new information regarding the toxicity of substances. According to the list, lead, mercury, and cadmium are the most toxic heavy metals, as well as being among the most toxic substances.

Table 2 Priority classification of some metal ions according to the US Agency for Toxic Substances and Disease Registry.

2013 Rank	Substance
2	Lead
3	Mercury
7	Cadmium
17	Chromium(VI)
43	Beryllium
51	Cobalt
57	Nickel

The extent of the health risk presented by cadmium compounds, as well as the actions issued by different countries, has spurred the development of alternative products since the 1990s [34].

There are two different types of toxicity: *acute* toxicity caused by sudden exposure to a large dose and *chronic* toxicity, which may be attributable to low-dose exposure over a long time. Each type causes different effects and symptoms. Acute and chronic intoxication caused by metal compounds has been described previously, and much information can be found in two extensive reviews [35,36].

Acute human cadmium poisoning is very rare and it is mainly due to the oral intake of cadmium compounds in suicide, accidental cadmium contamination of food items, or inhalation in the work place. The acute toxicity of cadmium leads to gastrointestinal effects (diarrhea and vomiting). The liver is the main organ affected and hepatotoxicity is the major cause of death [34,37–41]. Most acute intoxication occurs in work places, mostly because of the accidental exposure to high concentrations of cadmium oxide fumes (during soldering, flame-cutting of cadmium-coated metals, and in refining and smelting operations). Cadmium volatilizes readily during these processes because of its low boiling point (765 °C) and high vapor pressure, and it condenses into fine particles that react with oxygen to form breathable cadmium oxides. The main symptoms of acute intoxication due to cadmium fume inhalation are chemical pneumonitis and edema (with fatal consequences in many cases) [42,43], and hepatic and renal diseases [44]. The frequency of accidents in industrial environments, which were common in the past because of poor working conditions, has been reduced due to the improved hygiene and preventive measurements in work places, although some risks still exist in certain circumstances.

Chronic low-level cadmium intoxication depends on the specific local condition in terms of cadmium pollution. The general population may be exposed by eating cadmium-contaminated food (cereal products, grains, seafood, potatoes, and leafy vegetables) [45–48].

At present, the developing countries experience the most severe cadmium pollution problems from a dietary perspective [49]. In 2006, the average cadmium concentration in rice from polluted areas in Jiangxi Province, China was 0.59 mg/kg, which was 2.5 times higher than that in 1987 and about three times higher than the maximum allowable concentration required by the Chinese Hygienic Standard for rice (0.20 mg/kg) [50]. In 2007, a study conducted at a metal-polluted village in Vietnam showed that the cadmium concentration in rice was 0.31 mg/kg, which was also significantly higher than the maximum allowable concentration for cadmium in rice required by the Vietnamese Ministry of Health (0.20 mg/kg) [51]. Inhaling cigarette smoke is one of the major causes of chronic cadmium intoxication because cadmium is particularly easily absorbed via the respiratory tract, where cigarette smokers may absorb 10–40% of the inhaled

cadmium. Several recent studies have suggested a potential link between long-term, low-level environmental cadmium exposure and bone diseases [52–54].

In the 1950s, Japanese physicians reported the presence of a disease characterized by multiple fractures and distortion of the long bones among the population of the Jinzu River basin in Japan. The river water was highly contaminated by cadmium as well as by other toxic metal ions to a minor extent, and it was used to irrigate rice. Thus, the local population developed Itai-itai disease due to the consumption of this cadmium-contaminated rice [55–58]. Some plants are efficient cadmium bio-accumulators and when they are grown in high acidity, cadmium-rich soils (or in soils treated with cadmium-containing phosphate fertilizers), their consumption leads to a high cadmium content in the food chain [59,60]. Humans can consume cadmium directly in cadmium-containing vegetables or indirectly by eating animals fed with these vegetables. The European Community has determined that the normal dose for cadmium ingested from these two sources is 1–3 μg per day, which is not considered a hazardous level. The actual amount of cadmium absorbed depends greatly on the individual's nutritional status, where absorption is low in people with good nutrition in terms of essential metal ions (zinc, iron, and calcium), whereas those with low levels of essential metals absorb more of this dangerous element. Thus, the high incidence of Itai-itai disease in aged women was determined strictly by their low body iron content [61].

The toxic effects of chronic cadmium exposure manifest as insomnia, chronic rhinitis, anemia, emphysema, eosinophilia, osteoporosis, and irreversible renal tubular injury. Cadmium compounds cause damage to the kidneys and the central nervous system. They are also carcinogenic for connective tissues, the lungs, and liver, and are possibly teratogenic [62]. The kidney is the organ that is most exposed to chronic intoxication because cadmium accumulates in the kidney tubules and damages tubular cells [63]. The metallothioneins (MTs) found in these two organs have a high affinity for cadmium [64]. The liver and kidneys contain high-levels of MTs, which can act as a reservoir for cadmium, thereby protecting the body from the toxic effects of the free metal ion [65,66]. The discovery of MTs was critical for our understanding of cadmium toxicity. MTs comprise a group of proteins with the main function of storing and deactivating various metal ions. MTs can form high-affinity bonds with cadmium through cysteine residues. Thus, these metal-sequestering proteins can lower the cadmium concentration in critical tissues, and the presence of cadmium appears to induce the synthesis of these proteins in the liver and kidneys [67]. MTs are important for the detoxification of cadmium. After absorption, albumin transports cadmium in the blood to the liver, where it is bound to MTs. The Cd-MT complex is then released into the bloodstream and transported to the kidney [67]. The Cd-MT complex is filtered through the glomeruli and absorbed by the proximal tubules, where it accumulates in the kidney cortex, which contains most of the cadmium burden in the body [58]. The half-life of cadmium in the kidney is greater than 10 years [68,69] and there is a strong correlation between the cadmium content of the kidney and cadmium in urine [68]. Urinary cadmium is an indicator of the lifelong kidney accumulation, and thus the long-term cadmium burden in the body. Most of the cadmium circulating in the blood is bound to erythrocytes and the shorter half-life of cadmium in the blood makes the blood cadmium concentration a good biomarker for recent exposure [70]. Therefore, the presence of cadmium in the blood is a biological indicator of current exposure, whereas the urinary concentration is a measure of chronic exposure [71].

In addition to MTs, other endogenous molecules are important for cadmium metabolism. The high affinity of Cd(II) for sulfur allows this metal ion to replace Zn(II) in different biomolecules [72]. Cd(II) enters cells the cell membrane via zinc transporters such as ZIP8 (transports Cd(II) in the lungs, testes, and kidneys) and ZIP14 (transports Cd(II) in the liver and small intestine). These transporters are also found in the brain [73]. In addition, Cd(II) can be transported by other biomolecules that are specific to bivalent Fe(II) and Ca(II) ions. Cd(II) is not able to participate directly in redox reactions because of its electronic configuration, but it influences the Fenton reaction by displacing Fe(II) and Cu(II) ions from their binding sites in proteins [74]. The so-called Cd(II)-mediated oxidative stress damages neuronal cells and kidney proximal tubule cells [75,76]. The various mechanisms responsible for Cd(II)-induced carcinogenesis (disturbance of the DNA repair system, interaction with apoptotic pathways and cell proliferation, as well as epigenetic mechanisms) have been discussed previously [77].

4 Complex formation equilibria with amino acids

The toxicity of cadmium and its ability to compete with numerous metal ions in biological sites have prompted studies of its capacity to bind molecules of biological interest, such as amino acids, peptides, and proteins. This topic has been reviewed previously, with a particular emphasis on comparisons of the coordination ability of Cd(II) and Zn(II) [78]. Therefore, in this review, broad comparisons are made with other divalent metal ions of potential interest in biology as competitors with Cd(II) and Zn(II), such as Mn(II), Fe(II), Ni(II), and Cu(II). In addition, the number of amino acids considered has been restricted to 10, which represent the main categories of biogenic amino acids. Tables 3–10 show the corresponding protonation, complex formation, and metal-hydrolysis constants, from which the pM values were also computed [79]. The pM value allows the binding ability of different amino acids with the same metal ion to be compared, as well as the affinity of different metal ions for a specific ligand. The pM values were calculated for binary solutions where the total concentration of the ligand was 10^{-5} M and that of the metal was 10^{-6} M at pH = 7.4. Unfortunately, the experimental conditions under which the constants were measured were not identical due to the heterogeneity of the published data. However, qualitative comparisons are possible despite the variations due to temperature and ionic strength.

Table 3 Protonation constants of model amino acids [80,81].

	log K_1	log K_2	log K_3	log K_4	Temperature (°C)/ionic strength (M)	Refs.
Gly	9.58	2.36			25 °C/0.1	[80]
Val	9.49	2.26			25 °C/0.1	[81]
Phe	9.09	2.19			25 °C/0.1	[81]

L-Dopa	13.4	9.81	8.75	2.2	25 °C/0.1	[81]
Asn	8.72	2.15			25 °C/0.1	[81]
Ser	9.05	2.13			25 °C/0.1	[81]
Asp	9.62	3.70	1.94		25 °C/0.1	[81]
Lys	10.68	9.15	2.19		25 °C/0.1	[81]
His	9.10	6.04	1.81		25 °C/0.1	[80]
Cys	10.36	8.16	1.9		25 °C/0.1	[81]

Table 4 Complex formation constants of some model amino acids with the Zn(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [81–85].

	$\log \beta_{110}$	$\log \beta_{120}$	$\log \beta_{130}$	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	4.96	9.19	11.6	6.00	25 °C/0.1	[81]	
Val	4.46	8.24		6.00	25 °C/0.1	[83]	
Phe	4.25	8.25	–	6.00	25 °C/0.1	[81]	
L-Dopa	(3.96)[a]	–	–	6.00	25 °C/0.1	[82]	$\log \beta_{112} = 27.17$; $\log \beta_{122} = 37.87$; $\log \beta_{222} = 43.35$; $\log \beta_{121} = 28.45$; $\log \beta_{123} = 46.83$
Asn	5.07	9.43	12.30	6.02	25 °C/3.0	[81]	
Ser	4.60	8.5	–	6.00	25 °C/0.1	[81]	
Asp	5.69	9.77	–	6.01	25 °C/0.1	[84]	
Lys	6.32	–	–	6.00	25 °C/0.1	[85]	$\log \beta_{111} = 14.72$; $\log \beta_{122} = 28.85$; $\beta_{121} = 19.67$
His	6.51	12.04	–	6.21	25 °C/0.1	[81]	$\log \beta_{111} = 11.38$; $\log \beta_{122} = 23.51$; $\beta_{121} = 17.84$
Cys	9.17	18.12	–	6.78	25 °C/0.1	[81]	$\log \beta_{111} = 14.86$; $\log \beta_{122} = 29.96$; $\beta_{121} = 24.46$

[a] $\log \beta_{110} = \log \beta_{111} - \log K_2$.

Table 5 Complex formation constants of some model amino acids with the Cd(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [81,82,86–89].

	$\log \beta_{110}$	$\log \beta_{120}$	$\log \beta_{130}$	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	4.24	7.71	9.76	6.00	25 °C/0.1	[81]	
Val	3.69	6.86	–	6.00	25 °C/0.1	[86]	
Phe	3.7	6.9	–	6.00	25 °C/0.1	[81]	
L-Dopa	(3.04)[a]	–	–	6.00	25 °C/0.1	[82]	$\log \beta_{112} = 26.21$; $\log \beta_{123} = 45.62$
Asn	4.07	7.58	9.61	6.00	25 °C/3.0	[81]	
Ser	3.95	7.08		6.00	25 °C/0.1	[87]	

Asp	4.35	7.55	–	6.00	25 °C/0.1	[81]	
Lys	(3.70)[b]	(6.48)[b]	(9.24)[b]	6.00	25 °C/0.1	[88]	log β_{111} = 14.38; log β_{122} = 22.36; log β_{133} = 41.28
His	5.74	9.96	–	6.04	25 °C/0.1	[81]	log β_{111} = 11.17
Cys	12.82	21.71	27.52	10.39	25 °C/1.0	[89]	log β_{230} = 40.41

[a] log β_{110} = log β_{111} – log K_2.

[b] Protonated ligand (LH).

Table 6 Complex formation constants of some model amino acids with the Mn(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [81,90–94].

	log β_{110}	log β_{120}	log β_{130}	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	3.0	–	–	6.00	25 °C/0.1	[90]	
Val	2.34	3.97	5.19	6.00	37 °C/0.15	[91]	
Phe	2.94	–	–	6.00	25 °C/0.1	[92]	
L-Dopa	8.14	16.0	–	6.00	25 °C/0.1	[81]	log β_{111} = 17.76; log β_{122} = 37.0; log β_{121} = 27.32
Asn	3.10	5.22	–	6.00	25 °C/3.0	[81]	
Ser	2.50	3.98	–	6.00	25 °C/0.1	[81]	
Asp	3.7	–	–	6.00	25 °C/0.1	[81]	
Lys	(2.18)[a]	–	–	6.00	20 °C/0.01	[93]	log β_{111} = 12.86
His	3.32	6.29	–	6.00	25 °C/0.1	[81]	
Cys	4.56	–	–	6.00	25 °C/0.1	[94]	

[a] Protonated ligand (LH).

Table 7 Complex formation constants of some model amino acids with the Fe(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [81,93,95–101].

	log β_{110}	log β_{120}	log β_{130}	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	4.13	7.65	–	6.00	25 °C/0.1	[81]	
Val	3.39	–	–	6.00	20 °C/1.0	[95].	
Phe	3.74	7.19	10.7	6.00	25 °C/3.0	[96]	
L-Dopa	8.80	–	–	6.00	25 °C/0.1	[97]	
Asn	4.37	7.57	10.26	6.00	25 °C/3.0	[98]	
Ser	4.30	7.38	10.30	6.00	25 °C/3.0	[99]	
Asp	5.34	8.57	(h)	6.01	25 °C/0.1	[100]	

Lys	(4.5)[a]	–	–	6.00	20 °C/0.01	[93]	log β_{111} = 15.18
His	5.88	10.43	–	6.06	25 °C/3.0	[101]	
Cys	(6.2)[a]	–	–	6.00	20 °C/0.01	[93]	

[a] protonated ligand (LH).

Table 8 Complex formation constants of some model amino acids with the Ni(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [81,102–104].

	log β_{110}	log β_{120}	log β_{130}	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	5.78	10.58	14	6.02	25 °C/0.1	[81]	
Val	5.42	9.72	12.2	6.01	25 °C/0.1	[81]	
Phe	5.13	9.65	–	6.01	25 °C/0.1	[103]	
L-Dopa	(4.88)[a]	(8.9)[a]	–	6.02	25 °C/0.1	[81]	log β_{112} = 28.09; log β_{123} = 47.45; log β_{124} = 55.32; log β_{122} = 38.45; log β_{136} = 81.51; log β_{121} = 28.79; log β_{111} = 20.09; log β_{120} = 17.32
Asn	5.68	10.23	–	6.09	25 °C/0.1	[81]	
Ser	5.4	9.9	13.1	6.02	25 °C/0.1	[81]	
Asp	7.15	12.40	–	6.25	25 °C/0.1	[81]	log β_{111} = 11.20
Lys	5.75	10.34	–	6.01	25 °C/0.1	[104]	log β_{111} = 15.60; log β_{122} = 30.49; log β_{133} = 44.05; log β_{132} = 34.26
His	8.66	15.52	–	8.20	25 °C/0.1	[81]	log β_{111} = 12.28; log β_{121} = 20.55
Cys	9.83	20.19	–	8.44	20 °C/0.1	[102]	log β_{111} = 14.79; log β_{123} = 33.0; log β_{134} = 45.7

[a] Diprotonated ligand (LH_2).

Table 9 Complex formation constants of some model amino acids with the Cu(II) ion. The subscripts indicate the stoichiometric coefficients for the metal, ligand, and proton, respectively [80,81,102,105].

	log β_{110}	log β_{120}	log β_{130}	pM	Temperature (°C)/ionic strength (M)	Refs.	Other constants
Gly	8.11	14.96	–	7.06	25 °C/0.1	[80]	
Val	8.09	14.9	–	7.14	25 °C/0.1	[81]	
Phe	7.9	14.7	–	7.46	25 °C/0.1	[81]	
L-Dopa	(7.53)[a]	(14.3)[a]	–	8.19	25 °C/0.1	[81]	log β_{112} = 30.74; log β_{124} = 60.72; log β_{123} = 53.97; log β_{122} = 45.57; log β_{121} = 35.97; log β_{120} = 25.67
Asn	7.83	14.36	–	7.79	25 °C/0.1	[81]	log $\beta_{12\text{-}1}$ = 3.91; log $\beta_{12\text{-}2}$ = -8.09
Ser	7.89	14.5	–	7.43	25 °C/0.1	[81]	log β_{111} = 11.44; log $\beta_{12\text{-}1}$ = 4.69
Asp	8.88	15.87	–	7.78	25 °C/0.1	[81]	log β_{111} = 12.58; log β_{121} = 19.87; log β_{210} = 10.39; log β_{220} = 19.47
Lys	(7.49)[b]	(13.82)[b]	–	6.87	25 °C/0.1	[105]	log β_{111} = 18.17; log β_{122} = 35.18; log β_{121} = 25.27; log β_{120} = 14.83
His	10.16	18.14	–	10.54	25 °C/0.1	[80]	log β_{111} = 14.18; log β_{121} = 23.91; log β_{122} = 27.14; log $\beta_{22\text{-}2}$ = 8.03; log $\beta_{12\text{-}1}$ = 6.81

Cys[c]	–	–	–	–		[102]	

[a] Diprotonated ligand (LH_2).

[b] Protonated ligand (LH).

[c] Cys reduces Cu(II) to Cu(I).

Table 10 Metal ion hydrolysis at 25 °C. The subscripts indicate the stoichiometric coefficients for the metal and proton, respectively [106].

	$\log \beta_{1-1}$	$\log \beta_{1-2}$	$\log \beta_{1-3}$	$\log \beta_{1-4}$	$\log \beta_{2-1}$	$\log \beta_{2-2}$	$\log \beta_{2-3}$	$\log \beta_{2-6}$	$\log \beta_{4-4}$
Zn(II)	−9.0	−16.9	−28.4	−41.2	−9.0	–	–	−57.8	–
Cd(II)	−10.1	−20.4	−33.3	−47.4	−9.4	–	–	–	−32.9
Mn(II)	−10.6	−22.2	−34.8	−48.3	−10.6	–	−23.9	–	–
Fe(II)	−9.5	−20.6	−31	−46	–	–	–	–	–
Cu(II)	−8	−17.3	−27.8	−39.6	–	−10.6	–	–	–
Ni(II)	−9.9	−19	−30	−44	−10.7	–	–	–	−27.7

According to the calculated pM values, it is apparent that these amino acids are not particularly strong ligands for the divalent metal ions considered with a few exceptions, such as Cys for Cd(II) and Ni(II), and His for Ni(II) and Cu(II). It should be noted that low pM values indicate low affinity, where the lower limit for the pM value is 6, which corresponds to the p (=$-\log_{10}$) value of the total concentration of the metal (in this case, $C_{M,tot} = 10^{-6}$ M). Therefore, pM values close to 6 indicate that at pH = 7.4, almost all of the metal is free (i.e., not coordinated to the amino acid).

The low pM values for all of the amino acids (except Cys) are reflected by the fact that coordination starts only at pH > 5, and that the hydrolysis and precipitation of metal hydroxides is always observed at moderately alkaline pH values. In addition, the formation of hydroxo-complexes has never been reported. Excluding cysteine, with which Cd(II) has an outstanding affinity, the data in Tables 4–9 basically follow the Irving-Williams series [107], where Cd(II) has a similar affinity for amino acids as that of Fe(II): Mn(II) < Fe(II) ≈ Cd(II) < Zn(II) < Ni(II) << Cu(II). For cadmium, the speciation models in Table 5 predict the formation of mono-, bis-, and tris-complexes, where the ligand can be protonated if it contains a basic side chain, as found in L-Dopa, Lys, and His. Without considering the formation of tris-complexes, the stabilities of Cd(II) mono- and bis-complexes with different amino acids are very similar after subtracting the contribution due to the protonation of the side chain. Thus, the complex formation constants are not affected significantly by the nature of the side-chain, which can be either aliphatic, aromatic, or polar, and contain acidic or basic groups. The same is true for Met, which contains a thioether side group. This behavior may be explained by the fact that the coordination mode is the same for all of the amino acids, i.e., *Gly-like*, with the exceptions of Cys (as discussed later) and His, which contains an imidazole group with a high coordination capacity. His can bind metal ions with two nitrogens (amino and imidazole), thereby leading to the formation of a chelate six-membered ring, and with its carboxyl group, where it acts in a tridentate manner. The higher affinity for His by all metals is confirmed and the Irving-Williams series is satisfied.

The geometry of the Cd(II) complexes with amino acids is most likely to be octahedral, which agrees with observations made in the solid state by studying the crystals of [Cd(II)$(Gly)_2$] [108], [Cd(II)$(Met)_2$] [109], [Cd(II)$(Asn)_2$] [109], [Cd(II)$(Trp)_2$] [110], and [Cd(II)$(His)_2$] [111].

Cysteine is a special case because it contains a thiol group in its side chain. Cys has the ability to act as a tridentate ligand *via* its three donor groups ($-NH_2$, $-S^-$ and COO^-) to form (with respect to the *Gly-like* coordination mode) two additional chelate rings, which are five-membered (between N and S) and six-membered (between O and S), respectively. The Irving–Williams order is again satisfied regarding the stability of the Cys complexes formed with all the metals considered in this review. In this comparison, Cd(II) complexes were excluded because they have extraordinarily high stability due to the great affinity of this metal for the thiolate group. It should be noted that no reliable data are available regarding the complex formation constants for Cu(II) with Cys because these amino acids reduce Cu(II) to Cu(I) [112].

The polymeric structure of the complex [Cd(II)(L-Cys)]$_n$ in the solid state has been published [113]; it is formed by adjacent cadmium and sulfur ladders, and the thiolate groups of cysteines act as bridges between two Cd(II) ions. The ladders are bridged by the carboxylate groups of Cys, where the oxygen atoms are bound to two different cadmium ions. Cd(II) ions have an octahedral environment, which also involves the amino nitrogens of cysteines and they act as tridentate ligands. The structure of the [Cd(II)(L-Cys)]$_n$ polymer is shown in Fig. 1.

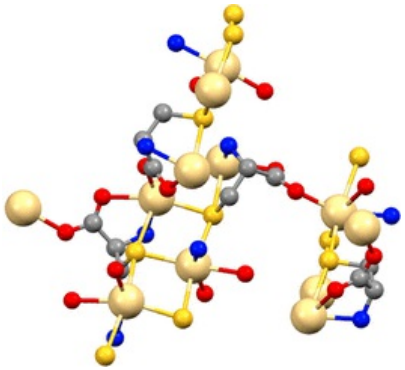

Fig. 1 Crystal structure of the polymeric complex $[Cd(II)(L\text{-}Cys)]_n$ [113]. Hydrogen atoms have been omitted for clarity. Color code: red = oxygen, blue = nitrogen, dark yellow = sulfur, gray = carbon, light yellow (big balls) = cadmium. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Figs. 2–4 show the distribution diagram for the Cd(II)/Cys system and the competition diagrams for the Cd(II)/Ni(II)/Cys and Cd(II)/Zn^{2+}/Cys systems, respectively. Clearly, at neutral pH, Cd(II) is able to sequester all of the cysteines in solution, even in the presence of equimolar amounts of Ni(II) or Zn(II).

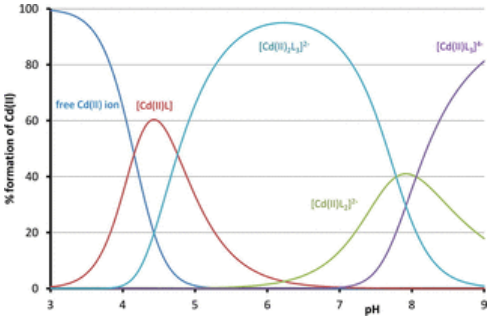

Fig. 2 Distribution diagram for the Cd(II)/Cys system at 25 °C and I = 0.1 M. $[Cd(II)]_{tot}$ = 0.001 M; M/L ratio = 1:3. Data from [89].

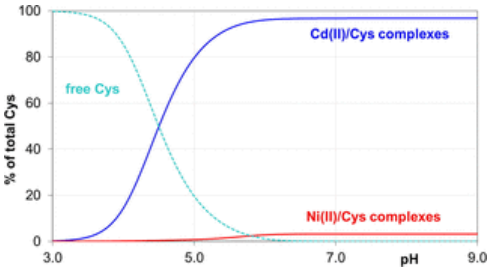

Fig. 3 Competition diagram for the Cd(II)/Ni(II)/Cys system at 25 °C and I = 0.1 M. $[Cd(II)]_{tot} = [Ni(II)]_{tot} = [L]_{tot}$ = 0.001 M. Data from [89,102].

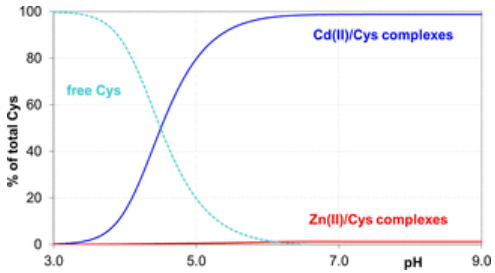

Fig. 4 Competition diagram for the Cd(II)/Zn(II)/Cys system at 25 °C and I = 0.1 M. $[Cd(II)]_{tot} = [Zn(II)]_{tot} = [L]_{tot} = 0.001$ M. Data from [81,89].

A more thorough discussion of the Cd(II) complexes with amino acids was provided previously [114] and this is outside the scope of this review.

5 Complex formation equilibria with peptides and proteins

In general, the chelating ability of peptides is due mainly to: 1) their N-and C-terminal groups if they are unprotected; 2) the side chains of the amino acid residues; 3) the amide and carbonyl groups in their polypeptidic backbone. For Cd(II), the Gly-like coordination with the N-terminal amino group and the neighboring carbonyl group, or the binding to the C-terminal carboxyl group do not lead to the high stability of complexes (and thus they are not of potential interest in biology). The same is true of the donor sites present in the side chains of amino acid residues, except His and Cys (see below) in a specific manner. In addition, some evidence was obtained only very recently regarding the ability of Cd(II) and Zn(II) to replace the amide protons in the polypeptide chain to bind nitrogen, as found frequently with Ni(II) and Cu(II).

5.1 His-containing peptides

The pyridine-like nitrogen atom of the His imidazole ring is one of the most effective and versatile donor atoms during the formation of metal complexes with peptides and proteins. The role of this “anchor” in His with respect to cadmium for the formation of complexes with short peptides has been clearly demonstrated in the case of protected prion-protein fragments containing only one histidine residue [115,116], although the stability of these complexes was lower than that of the corresponding Zn(II), Ni(II), and Cu(II) species. Similar results were also obtained for unprotected peptides at their amino-terminus [78,117,118].

Metal complexes with poly-His peptides have recently attracted much interest due to the presence of several imidazole binding sites, which are available for simultaneous coordination with the metal ion, thereby leading to the formation of highly stable complexes, even when the amino terminus is protected. This behavior has been verified commonly for the metals that are studied most widely and are most interesting from a biological viewpoint, such as Cu(II) and Zn(II), but it also applies to Cd(II) [119]. A typical feature of these peptides is the formation of macrochelates where the metal is bound to two or more His residues. The formation constants measured for these complexes increase with the number of His residues and they are much higher than those recorded for complexes formed by protected mono-His-containing ligands, although lower than those recorded for Zn(II), Ni(II), and Cu(II) [114]. Despite the improved stability of the complex, the presence of poly-His ligands in solution cannot prevent the hydrolysis of Cd(II) and its subsequent precipitation at alkaline pH.

The similar behavior of Cd(II) and Zn(II), and the possibility of using $^{111/113}$Cd isotopes as NMR probes instead of Zn(II) has promoted investigations of the interactions between Cd(II) and proteins. One of the first proteins to be considered was albumin [120,121], which is the most abundant protein in blood, and cerebrospinal fluid, which is one of the most important carriers of metal ions in the plasma, as well as other proteins such as α-macroglobulin [120,122], His-rich glycoprotein, and ceruloplasmin [122].

A long series of studies of the interactions between albumin and metal cations [123–127] demonstrated that albumin contains at least four specific metal-binding sites with differences in selectivity, as follows.

1) The N-terminal site characterized by the Asp-Ala-His- sequence, which is also called the “ATCUN motif” (amino terminal copper and nickel binding motif).
2) The amino acid Cys-34 is the first cysteine residue in the chain and the only one of the 35 present in the sequence that is not involved in disulfide bridges.
3) A poly-His sequence located at the interface between domains I and II of the protein, which is called the “multi-metal binding site” (MBS) or “site A.”
4) The so-called “site B,” the position and sequence of which are not clear at present.

NMR studies using $^{111/113}$Cd isotopes [123,128,129] have shown that albumin has two thermodynamically equivalent sites for cadmium, which do not correspond to the ATCUN motif (the main coordination for Cu(II) and Ni(II)) or the Cys-34 residue (despite expectations), which instead has high affinity for Au(I) and Pt(II). The preferential coordination sites for Cd(II) and Zn(II) are site A (MBS) and site B. Moreover, an excess of Cu(II) can move Cd(II) from site A to an unidentified site C [123]. Site A contains several His residues, including His-67, where the latter was identified by mutagenesis experiments (His67Ala) [125]. Other residues that participate in the coordination of Cd(II) and Zn(II) at site A are His-247, Asn-99, and Asp-249, which form a trigonal bipyramidal structure where the fifth ligand is H_2O or Cl^- if present at high concentrations (Fig. 5). Site B for cadmium coordination has not yet been localized, but its affinity for Cd(II) is similar to that of site A, with a dissociation constant of 3 μM [127].

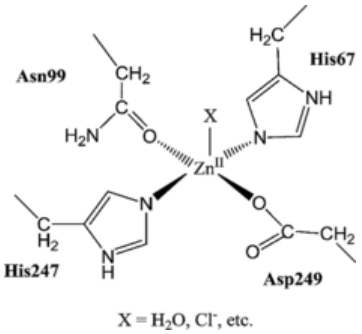

Fig. 5 Structure of the Zn(II) complex with the MBS/site A in albumin, according to [125].

Several spectroscopic methods have been used to investigate the structural changes in albumin induced by a Cd(II) salt [130,131]. The binding of cadmium acetate to albumin alters its conformation, thereby causing partial unfolding and inducing aggregation.

A size-exclusion chromatographic method coupled with flame atomic absorption spectrophotometry was employed to investigate the effect of competition between albumin and low molecular weight ligands in the coordination with Cd(II) [132]. It was shown that His and oxidized glutathione (although four times in excess) could not mobilize the cadmium ion from its complex with albumin, but 70% of the metal was mobilized by N-acetyl-L-cysteine, and nearly 100% by Cys and reduced glutathione (GSH), at physiological pH. These equilibria may be relevant for the mechanisms responsible for Cd(II) transfer from the blood to target tissues.

5.2 Thiol-containing peptides

As mentioned earlier in the description of Cd(II) complexes with amino acids, it is widely accepted that Cd(II) has a clear preference for thiolate groups, where it usually has a higher affinity for them than Zn(II) ions. In biology, this implies a high affinity of Cd(II) for Cys-rich peptides.

In the case of oligopeptides, after anchoring the thiol group, metal chelation can proceed with the participation of the N-or C-termini, or even other sites containing donor atoms such as oxygen or nitrogen belonging to the lateral groups of amino acidic residues. A systematic study of Cys-containing oligopeptides showed that the stability of these chelates follows the order: (S, N, O) > (S, N) > (S, O, O) > (S, O) [133], but the coordination mode also depends on whether Cys is close to the carboxyl or amino terminus [134].

The most important low molecular weight ligand for Cd(II) is GSH, which is a non-protein tripeptide with the sequence: γ-Glu-Cys-Gly. GSH is very abundant in biological fluids, with intracellular concentrations up to 10 mM [135]. GSH is involved in many biological processes and one of the most important is protecting against reactive oxygen species. GSH contains eight potential donor atoms, which belong to the thiol group of Cys, the amino- and carboxylic-terminal groups, and the side chain of Glu and peptide groups. Thus, GSH can chelate a number of metals with high affinity.

GSH complexes with Cd(II) have been determined in thermodynamic (potentiometric) [137,138], spectroscopic [139–142], and theoretical (density functional theory) [131,143,144] studies, thereby demonstrating the presence of a large number of stoichiometries and geometries, which depend mainly on the pH and the metal-ligand ratio. The proposed speciation model in solution [145] contains both the mono-and bis- complexes with various protonation degrees (Tables 10 and 11; Fig. 6).

Table 11 First section: overall protonation (log β) and step deprotonation (pK_a) constants for GSH (L^{3-}) and the site involved in the acid-base equilibrium. Second section: overall complex formation constants (log β) and step deprotonation constants (pK_a) for the complex species in the Cd(II)/GSH system. All data were measured at 25 °C and I = 3.0 M [136].

Species	Log β	pK_a	Residue
LH^{2-}	9.88	9.88	SH
LH_2^-	19.04	9.16	NH_3^+
LH_3	22.86	3.82	COOH
LH_4^+	25.46	2.60	COOH

[CdLH]	17.02	6.84	–
$[CdL]^{-}$	10.18	9.89	–
$[CdLH_{-1}]^{2-}$	0.29	–	–
$[CdL_2H_2]^{2-}$	33.03	7.94	–
$[CdL_2H]^{3-}$	25.09	9.74	–
$[CdL_2]^{4-}$	15.35	12.18	–
$[CdL_2H_{-1}]^{5-}$	3.17	–	–

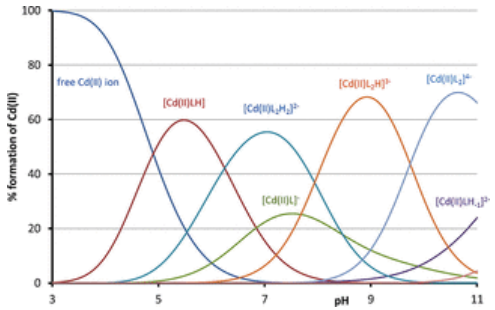

Fig. 6 Distribution diagram for the Cd(II)/GSH system at 25 °C and I = 3.0 M. $[Cd(II)]_{tot}$ = 0.001 M; M/L ratio = 1:2. Data from [136].

The main coordination site is the thiolate group assisted by the C-terminal carboxylate. There is no experimental evidence for the participation of amide groups belonging to the polypeptide backbone. An identical speciation model was proposed for Zn(II), but the stability of the complexes formed by this metal was lower than that for Cd(II) species, as shown by the competition diagram in Fig. 7.

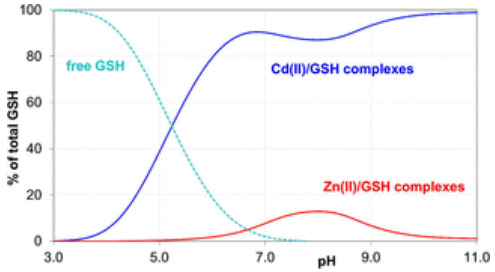

Fig. 7 Competition diagram for the Cd(II)/Zn(II)/GSH system at 25 °C and I = 3.0 M. $[Cd(II)]_{tot} = [Zn(II)]_{tot} = [GSH]_{tot}$ = 0.001 M. Data from [136].

Useful models for studying the complex formation solution equilibria between Cd(II) and proteins, such as MTs, phytochelatins or zinc-fingers, are represented by poly-Cys peptides, where the sequence matches the chelation sites of the proteins.

The first studies in this area used spectroscopic and electrochemical methods to investigate the hexapeptide KCTCCA, which corresponds to the C-terminus of mouse liver MTs [146–148]. This peptide is characterized by the presence of three cysteine residues in the sequence -CXCC- and it forms a particularly stable binuclear complex with Cd(II) ions.

The binding site present in the MT extracted from rabbit livers contains instead four cysteines, which are organized in the sequence of ICKGASDKCSCCA: the corresponding peptide, protected at both terminai, forms a mono-nuclear Cd(II) complex and the metal is bound to the four thiolate groups [149].

If the number of cysteines in the coordination site is important for determining the structure and stability of the complexes formed, then their positions in the peptide sequence can be crucial. De Silva et al. studied the behavior of three 18-mer peptides, containing the sequences -CAAC-, -CACA-, and -CCAA as active sites, as ligands for several metal cations [150]. The results showed that a peptide containing -CACA- binds cadmium with 10 times greater strength than a peptide containing the sequence -CAAC-

. However, it was notable the peptide -CCAA- could only bind the Hg(II) ion among all of the metals considered (i.e. not Cu(I), Zn(II), Cd(II), Ag(I), Ni(II), and Ca(II)), which demonstrates that the stability as well as the selectivity of peptidic ligands is influenced by the position of the amino acid residues that contain the donor atoms.

Two protected dodecapeptides inspired by the metal binding domain of some MerR metalloregulatory proteins, i.e., Ac-SCHGDQGSDCSI-NH_2 [151] and Ac-SCPGDQGSDCSI-NH_2 [152], have been synthesized and studied potentiometrically and spectroscopically. The formation of Cd(II) complexes with loop structures was demonstrated for the first peptide, where both the thiol groups of cysteines and imidazole in His participate in the coordination. However, at pH values close to neutral, mono-complexes (2S, N_{Im}, O) are formed if the M:L ratio is 1:1, where the oxygen probably belongs to a water molecule. On the contrary, if the metal:ligand molar ratio is 1:2, the formation of metal-bridged bis-complexes occurs with a (2S, $2N_{Im}$) or (4S) environment around the metal ion, where the donor atoms are derived from the cysteines and histidines of two different peptide molecules. His is not present in the sequence of the second peptide and it is replaced by proline. The chelating properties of this peptide against toxic metals such as Cd(II) and Hg(II) were investigated to determine the possibility of using it as a capturing agent for practical applications. In addition, the complex formation equilibria with Zn(II) were investigated for comparison. Mono- and bis- complexes are also formed with this ligand according to the metal-to-ligand ratio. In the case of Cd(II), the metal binds to cysteines and the carboxylate side group of one of the aspartic acid residues participates. In order to confirm whether the Zn(II) ion is capable of preventing the coordination of toxic metals to the peptide Ac-SCPGDQGSDCSI-NH_2, a solution containing Zn(II) and the peptide at a ratio of 1:1 was titrated with Cd(II) or Hg(II) at neutral pH. In the case of cadmium, the partial removal of Zn(II) from its mono-complexes was obtained, with the possible formation of ternary species. The complete removal of zinc was obtained only after the addition of a twofold excess of cadmium, with the formation of a binuclear complex of Cd(II). However, titrating with Hg(II) was sufficient to obtain a ratio of 1:1 between Hg(II) and Zn(II), thereby completely removing zinc from its complexes.

The metal binding ability has been characterized thermodynamically and spectroscopically for three peptides, i.e., Ac-GCASCDNCRACKK-NH_2, Ac-GCASCDNCRAAKK-NH_2, and Ac-GCASCDNARAAKK-NH_2, the first of which contains two -CXXC- motifs whereas the others have one or two cysteines substituted by alanine [153]. Thiol groups are always involved in the formation of complex species, the stability of which is determined largely by the number of sulfur atoms that bind to the metal. Asp and Lys residues do not participate in complexation. The following order of stability was verified in terms of the selectivity for various metal ions: Bi(III) ≫ Cd(II) > Zn(II) > Ni(II). This study was subsequently extended to the cyclic peptide GCASCDNCRACKK [154]. In the case of Cd(II) and Ni(II), this peptide forms significantly more stable complexes than those of its linear analogue over the entire pH range considered. By contrast, the Zn(II) complexes with cyclic peptide are more stable only up to neutral pH and the stability order is reversed at alkaline pH. This difference in behavior between Cd(II) and Zn(II) is related to the size of the two metal ions as well as the cyclic-ligand rigidity, where cadmium is more bulky so it can bind four sulfur atoms, whereas zinc can only coordinate three of them.

The same metals were used to investigate the binding ability of a cysteine-rich decapeptide (MPGCPCPGCG-NH_2) corresponding to the N-terminal fragment of the ZIP13 zinc transporter, which contains three Cys residues and the unprotected N-terminus [155]. Again, the main coordination sites of all the metals were sulfur atoms in the deprotonated thiol groups. In the case of Zn(II) and Cd(II), at basic pH, it was shown that the N-terminal amino group also participates in coordination as the fourth donor site (Fig. 8). The stability of the complexes as a function of the nature of the metal follows the same order listed above: Bi(III) ≫ Cd(II) > Zn(II) > Ni(II).

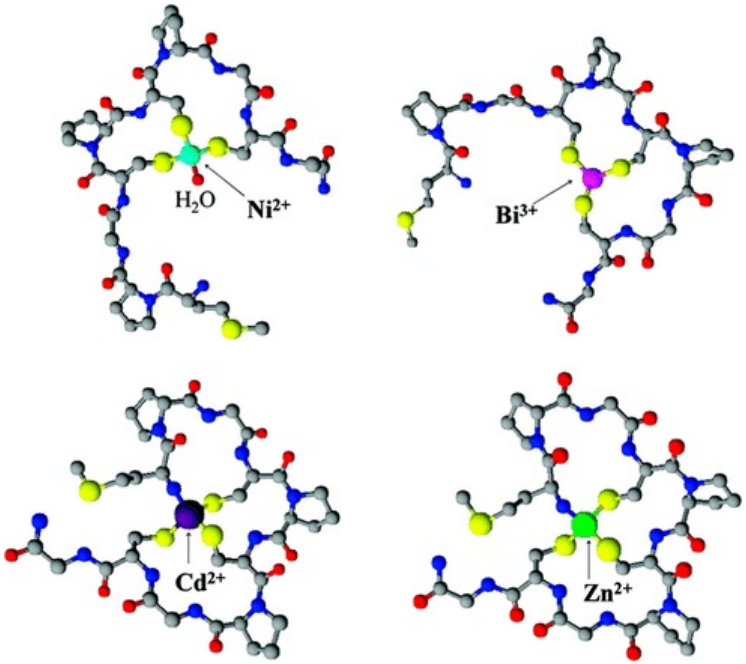

Fig. 8 Proposed structures of metal complexes formed by the N-terminus of ZIP13 (MPGCPCPGCG–NH_2). Reproduced from Ref. [155] with permission.

The coordination pathways of the two peptides, CSSACS-NH_2 and ACSSACS-NH_2, in the presence of Zn(II) and Cd(II) have been studied recently [156]. The presence of cysteine as the N-terminal residue of the hexapeptide promotes the formation of a five-membered ring containing the amino nitrogen and thiolic sulfur. The coordination of the second sulfur belonging to the Cys-5 residue completes the coordination sphere, thereby forming macrochelates where the mono-complexes are more stable for Cd(II) than for Zn(II). If the same metal ion is considered, the hexapeptide complexes are more stable than those formed by the heptapeptide ACSSACS-NH_2, where an additional Ala residue replaces cysteine as the terminal amino group. In the case of the heptapeptide, metal chelation starts with the formation of protonated mono- and bis- complexes where the only donors are sulfur atoms. The terminal amino group participates in coordination only at alkaline pH, where deprotonated species are formed. Spectroscopic results obtained for these complexes suggest, in the case of both Zn(II) and Cd(II), the deprotonation/coordination of the amide group of the peptide bond between Ala-1 and Cys-2, which is promoted by the proximity of the peptide backbone to the metal ion due to the simultaneous coordination of both the N-terminal nitrogen and the sulfur atom of Cys-2. It should be noted that this is one of the rare situations where Zn(II) is claimed to interact with amide nitrogen atoms and the first reported case where this behavior has been attributed to Cd(II).

It is not unusual that a coordination site of Zn(II) and Cd(II) contains both His and cysteine residues, as found in some retroviral-type zinc-finger peptides [157] or embryo-specific zinc-binding MTs from wheat [158], which exhibit selectivity for Cd(II) and Zn(II) depending on the coordination mode, (4S) or ($2S,2N_{im}$). The participation of His residues helps to stabilize the complex species with MTs by decreasing the overall charge to favor the formation of H-bonds and reducing the number of disulfide bonds [159]. The replacement of His with other amino acids containing potential coordinating side groups, such as Asp, can change the structure and stability of complexes dramatically [160].

Helicobacter pylori is a pathogenic bacterium, which can colonize the mucous membranes of the stomach to cause gastritis and ulcers. Its survival is facilitated by the production of ammonia via the hydrolysis of urea, which buffers the surrounding highly acidic environment. This process requires the synthesis of two nickel-containing enzymes, urease and [NiFe] dehydrogenase, as well as some proteins that are required to supply nickel, such as Hpn, HypA and its partner HypB, and heat shock protein A (HspA). All of these proteins possess His- and Cys-rich domains, which are suitable for the coordination of metal ions [161]. Kozlowski et al. [162] studied the metal complexing properties of the following three protected decapeptides: Ac-CCSTSDSHHQ-NH_2, Ac-EEGCCHGHHE-NH_2, and Ac-GSCCHTGNHD-NH_2, which correspond to the binding sites of Hpn and HspA, and they contain the -Cys-Cys- motif together with two or three additional His residues in variable positions. The fundamental role of the thiol group of cysteine was confirmed, which leads to the formation of mono-and bis- complexes of Zn(II) and Cd(II) with the donor atom sets (2S), (3S), or (4S), depending on the pH, presumably with a tetrahedral geometry. Instead, Ni(II) forms square planar species with these ligands, where the deprotonated amide nitrogens in the peptide chain also participate. Surprisingly, the Ni(II) complexes are more stable than those of Zn(II) regardless of the pH, which disagrees with many previous reports (see above). It is likely that the His residues are partially responsible for this behavior, although this issue has not been explored.

The metallochaperone HypA secreted by *Helicobacter pylori* contains at least two metal-coordination sites: one for Ni(II) located in its N-terminal portion and the second for Zn(II) situated in the C-terminal domain [161]. The latter, which corresponds to

the sequence -ELECKDCSHVFKPNALDYGVCEKCHS-, includes four cysteine residues at positions 74, 77, 91, and 94 arranged in two -CXXC- motifs, and two histidines in positions 79 and 95. ^{113}Cd NMR, potentiometric, and spectroscopic data indicate that these sulfur atoms are the basis of coordination for Zn(II) [161,163], but the imidazole nitrogens can also participate in the coordination at acidic pH. In order to clarify the role of histidine molecules in the formation of Cd(II), Zn(II), and Ni(II) complexes with the C-terminal region of HypA, four decapeptides were synthesized, which included the first or the second -CXXC- motif, with either the neighboring His residues (79 or 95) as in the wild-type sequence, or with Ser instead of His [164]. These model peptides form mono- and bis- complexes of Cd(II) and Zn(II) where the donors are the two thiolic sulfur atoms and the imidazole nitrogen when it is present in the sequence. The complexes are more stable when His is separated from the second Cys residue by a serine compared with that where Cys and His appear consecutively. Some stability is lost when His is replaced by Ser. The same study determined the behavior of the model peptide Ac-ELECKDCSHVFKPNALDYGVCEKCHS-NH_2, which corresponds to the full zinc coordination site of HypA, and its analogues as ligands, where the length and the sequence of the linker that joins the two binding motifs -CXXC- were varied. These peptides form macrochelates with Cd(II) and Zn(II), with 1:1 stoichiometry and coordination modes (2S, $2N_{im}$) at acidic pH and (4S) around pH 8. The cadmium complexes are considerably more stable than those with zinc, and the stability of the complexes decreases as the length of the linker increases.

Finally, it should be mentioned that a *de novo* protein design strategy was recently applied to the construction and study of metal binding sites, thereby overcoming the problems caused by the use of both oversimplified short model peptides and very complex full-length proteins. This strategy was reviewed recently in the case of Cd(II) complexes [165].

The interactions between Cd(II) and full-length proteins, such as zinc-finger proteins, MTs, or phytochelatins, are beyond the scope of the present review, and thus they are not discussed further. However, recent excellent reviews are available for the interested reader [166,167].

6 Recent developments in chelation therapy for cadmium

As discussed earlier, the toxicity of cadmium demonstrates the clinical requirement for a chelation treatment to scavenge aged cadmium deposits from the liver and kidneys.

Only a few studies have described clinical chelation treatments for cadmium toxicity, but numerous animal experiments have been performed to develop chelation approaches [168–171].

A recent review explained the inherent problem of cadmium chelation, where the complex formation constants for cadmium and zinc are almost equal, and thus each chelator for toxic cadmium can also act on endogenous zinc [172]. Therefore, cadmium chelation is perturbed by the far greater concentration of the essential metal ion.

The toxicokinetics of cadmium make the effective, long-term chelation of deposited cadmium a serious problem. After it enters the body, cadmium is found within cells and mainly in the liver where it is bound by MTs. The Cd-MT complex is then transferred by the blood circulation to bone and the kidneys, where it is deposited in the proximal tubular cells, thereby causing tubular cell necrosis and subsequent urinary loss of filterable proteins, calcium, and small molecules, and thus the manifestation of the effects of chronic cadmium intoxication [67]. These unusual toxicokinetics are responsible for the failure of hydrophilic chelating agents during the treatment of acute cadmium poisoning [173]. Different chelating agents from several families of chemical compounds have been studied in animal experiments of acute cadmium intoxication (Table 12).

Table 12 Acronyms and IUPAC names of chelating agents for Cd(II) intoxication.

Acronym	IUPAC name
BAL	2,3 dimercaptopropan-1-ol
Deferiprone	3-Hydroxy-1,2-dimethylpyridin-4(1H)-one
Deferasirox	4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid
DMSA	Meso-2,3-dimercaptosuccinic acid
DMPS	2,3-dimercapto-1-propanesulfonic acid
DTPA	Diethylenetriaminepentaacetic acid
Monensic acid	4-[2-[5-ethyl-5-[5-[6-hydroxy-6-(hydroxyl methyl)-3,5-dimethyl-oxan-2-yl]-3-methyl-oxolan-2-yl]oxolan-2-yl]- 9-hydroxy-2,8-dimethyl-1,6-dioxasp iro[4.5]dec-7-yl]-3-methoxy-2-methyl-pentanoic acid
TTHA	Triethlenetetraminehexaacetic acid

The use of lipophilic chelators was found to increase cadmium toxicity in rabbits [174], but studies of hydrophilic chelators such as DMSA and DTPA, as well as polyaminopolycarboxylic acids, showed that these molecules were effective in both increasing cadmium excretion and reducing its toxicity [175–179].

All of these studies were performed in experimental conditions, which were limited to the injection of the toxic metal ion and the chelator. Experimental conditions similar to oral cadmium intoxication in humans were studied by Andersen

et al. [180–182], who demonstrated that the oral administration of chelators (DMSA, DMPS, DTPA, or TTHA) after the administration of a consistent oral cadmium dose could decrease intestinal cadmium absorption and the associated pathological consequences. To understand the mobilization of cadmium depots, Saric et al. [183] investigated the scavenging effect of orally administered DMSA and parenteral Ca-DTPA, which showed that DMSA was more effective than Ca-DTPA at removing cadmium from kidney and liver depots, where combined treatment with these two chelators was more effective.

The efficacy of some more lipophilic derivatives of DMSA (monoalkylesters and monoalkylamides) [184–186] was demonstrated for the removal of aged cadmium depots, but they are too toxic for potential applications in clinical treatments.

The results of early animal experiments, particularly those of the well-planned experiments performed by Andersen, indicate that the treatment of choice for acute oral human cadmium intoxication should be based on either oral DMSA administration or parenteral calcium DTPA administration, whereas the BAL and DDC treatments have too many disadvantages [180,187,188].

In recent years, ligands with completely different chemical structures and interesting properties have been tested in animal studies of the treatment of cadmium intoxication. Deferasirox was the last oral iron chelator introduced into clinical practice, and Saljoogi and Fatemi [189] showed that it reduced the blood cadmium levels in weanling rats. Deferasirox and deferiprone oral treatments (singly or combined) were studied by Fatemi et al. [190], who demonstrated that both of these chelating agents are effective for removing cadmium from different organs (kidneys, liver, and heart), but the combined treatment is most effective. The tetraethyl-ammonium salt of monensic acid, an antibiotic used in ruminant animal feeds [191], was tested in cadmium-treated mice by Ivanova et al. [192], who found that this chelator is effective in removing cadmium from different organs (kidneys, liver, heart, lungs, spleen, and testes). The same study also reported the X-ray structure of the 1:2 complex formed between cadmium and monensic acid [193] (Fig. 9), but no data were provided regarding the stability of this complex and analogous zinc complexes.

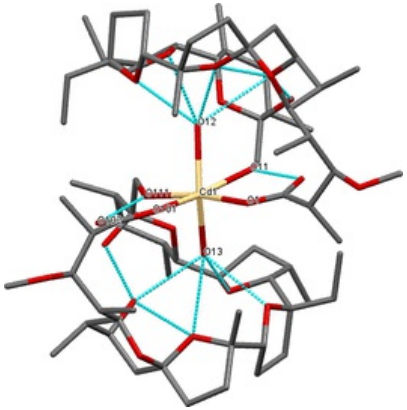

Fig. 9 Structure of the complex between cadmium and monensic acid (CCDC 754039).

Recently, Tang et al. [194] reported the synthesis of a new compound, sodium (S)-2-(dithiocarboxylato((2S,3R,4R,5R)-2,3,4,5,6 pentahydroxyhexyl)amino)-4-(methylthio) butanoate (GMDTC), which is not very toxic but it is highly efficient at removing Cd(II) from animal kidneys (in mice, rats, and rabbits). The Cd(II) scavenging activity suggests the support of glucose transporters in renal tubular cells. The formation of a $[Cd(GMDTC)_2]^{2-}$ complex was proposed based on HPLC-MS experiments and density functional theory calculations, although stability data were not reported based on the solution equilibrium studies. According to Tang et al., the characteristics of GMDTC make it an ideal chelating agent for treating the adverse effects of chronic cadmium exposure.

7 Conclusions

Due to their unique characteristics, cadmium compounds have a growing number of applications in various human activities. However, since the end of the last century, awareness of the extremely high toxicity of this metal and its compounds has led to the imposition of increasing limits on its use by international regulations. Nonetheless, cadmium exposure is still a major global health problem.

The competition between cadmium and other metals in vivo is one of the main explanations for cadmium toxicity, but the mechanisms that allow Cd(II) to be transported to various organs and tissues in humans are poorly understood. The most significant structural and equilibrium results concerning the interactions of Cd(II) with amino acids, peptides, and proteins, have been presented in this review and thoroughly compared with those of the other main bivalent metal ions, i.e., Zn(II), Cu(II), Fe(II), Mn(II), and Ni(II).

Chelating agents are almost the only tool for counteracting the adverse effects of chronic cadmium exposure. Given the current lack of adequate chelation therapy to effectively combat cadmium toxicity in humans, it is necessary to

conduct further research to design, synthesize, and characterize new non-toxic, effective cadmium chelators, as well as obtaining a better understanding of the behavior of cadmium in living organisms. As stated recently regarding the treatment for metal intoxications, "*the achievements are still inadequate to effectively counteract metal induced diseases, and a joint effort of chemical, biochemical, pathological, and clinical researchers might be appropriate to solve the related clinical problems, supported by large investments by central governments and international health organizations*" [195].

References

[1]

M.E. Weeks, *J. Chem. Educ.* **10**, 1933, 302–306.

[2]

M.A. Zoroddu, S. Medici, A. Ledda, V.M. Nurchi, J.I. Lachowicz and M. Peana, *Curr. Med. Chem.* **21**, 2014, 3837–3853.

[3]

R.G. Pearson, *J. Chem. Sci. Bangladore* **117**, 2005, 369–377.

[4]

R.G. Pearson, *J. Am. Chem. Soc.* **85**, 1963, 3533–3539.

[5]

G. Schwarzenbach, *Helv. Chim. Acta* **35**, 1952, 2344–2359.

[6]

D. Tuck, *Rev. Inorg. Chem.* **1**, 1979, 209–243.

[7]

M. Borsari, In: *Encyclopedia of Inorganic and Bioinorganic Chemistry* 2006, John Wiley & Sons Ltd..

[8]

M. Borsari,, In: *Encyclopedia of Inorganic and Bioinorganic Chemistry* 2014, John Wiley & Sons Ltd..

[9]

F.A. Cotton, G. Wilkinson, C.A. Murillo, M. Bochmann and R. Grimes, Advanced Inorganic Chemistry, 1999, Wiley; New York.

[10]

F. Basolo and R.G. Pearson, Mechanisms of Inorganic Reactions: A Study of Metal Complexes in Solution, 1967, John Wiley and Son; New York.

[11]

Cadmium, Minerals Yearbook, 2016, USGS (U.S. Geological Survey), <http://minerals.usgs.gov/minerals/pubs/commodity/cadmium/> 1st March 2016.

[12]

([<https://setis.ec.europa.eu/mis/material/cadmium> (6 June 2016)]).

[13]

United Nations Environment Programme, Final review of Scientific Information on Cadmium,

2010, <http://www.unep.org/hazardoussubstances/Portals/9/Lead_Cadmium/docs/Interim_reviews/UNEP_GC26_INF_11_Add_2_Final_UNEP_Cadmium_review_and_apppendix_Dec_2010.pdf>.

[14]

T.L. Rowbotham, The Art of Landscape Painting in Water Colours, 1850, Windsor and Newton.

[15]

A. Roy, *Natl. Gallery Tech. Bull.* **28**, 2007, 58–68.

[16]

I. Fiedler and M. Bayard, Cadmium yellows, oranges and reds, In: *Artists' Pigments; A Handbook of their History and Characteristics,* 1986, National Gallery of Art, 65–108.

[17]

B. Leone, A. Burnstock, C. Jones, P. Hallebeek, J. Boon and K. Keune, In: *Triennial Meeting (14th), The Hague, 12-16 September 2005,* 2005, James & James, 803–813.

[18]

G. Van der Snickt, J. Dik, M. Cotte, K. Janssens, J. Jaroszewicz, W. De Nolf, J. Groenewegen and L. Van der Loeff, *Anal. Chem.* **81**, 2009, 2600–2610.

[19]

M. Cook, Inorganic Pigments. Environmental Issues and Technological Opportunities, Industrial Inorganic Chemicals Group, 1994, Royal Society of Chemistry; London.

[20]

M. Barak, Electrochemical Power Sources: Primary and Secondary Batteries, 1980, IET.

[21]

V. Pop, H.J. Bergveld, D. Danilov, P.P. Regtien and P.H. Notten, Battery Management Systems: Accurate State-of-Charge Indication for Battery-Powered Applications, 2008, 181–220.

[22]

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:266:0001:0014:en:PDF>.

[23]

<http://eur-lex.europa.eu/legal-content/IT/TXT/?uri=CELEX%3A31991L0338>.

[24]

<https://www.euractiv.com/section/climate-environment/news/pvc-industry-presents-progress-report-on-voluntary-agreement/>.

[25]

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:134:0002:0005:en:PDF>.

[26]

M.T. Lecler, F. Zimmermann, E. Silvente, F. Clerc, A. Chollot and J. Grosjean, *Waste Manage.* **39**, 2015, 226–235.

[27]

J. Peng, L. Lu and H. Yang, *Renewable Sustainable Energy Rev.* **19**, 2013, 255–274.

[28]

V. Fthenakis, S. Morris, P. Moskowitz and D. Morgan, *Prog. Photovoltaics Res. Appl.* **7**, 1999, 489–497.

[29]

P. Sinha, C.J. Kriegner, W.A. Schew, S.W. Kaczmar, M. Traister and D.J. Wilson, *Energy Policy* **36**, 2008, 381–387.

[30]

C. Williams and D. David, *Soil Res.* **11**, 1973, 43–56.

[31]

F.M. Morel and E.G. Malcolm, *Metal Ions Biol. Syst. J.* **43**, 2005, 195–219.

[32]

International Agency for Research on Cancer, World Health Organization, IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1993, Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry, IARC.

[33]

<http://www.atsdr.cdc.gov/SPL/>, 1st April 2015.

[34]

G.F. Nordberg, *Toxicol. Appl. Pharmacol.* **238**, 2009, 192–200.

[35]

J. Aaseth, M.A. Skaug and J. Alexander, General chemistry of metal toxicity and basis for metal complexation chap 1, In: J. Aaesth, G. Crisponi and O. Andersen, (Eds.), *Chelation Therapy in the Treatment of Metal Intoxication,* 2016, Elsevier; London.

[36]

G. Crisponi, V.M. Nurchi, M. Crespo-Alonso and L. Toso, *Curr. Med. Chem.* **19**, 2012, 2794–2815.

[37]

P.L. Goering and C.D. Klaassen, *Toxicol. Appl. Pharmacol.* **70**, 1983, 195–203.

[38]

I.M. El-Ashmawy and S.A. Youssef, *Toxicol. Appl. Pharmacol.* **161**, 1999, 34–39.

[39]

J.M. Sauer, M.P. Waalkes, S.B. Hooser, R.K. Kuester, C.A. McQueen and I.G. Sipes, *Toxicology* **121**, 1997, 155–164.

[40]

L. Järup and A. Åkesson, *Toxicol. Appl. Pharmacol.* **238**, 2009, 201–208.

[41]

J. Godt, F. Scheidig, C. Grosse-Siestrup, V. Esche, P. Brandenburg, A. Reich and D.A. Groneberg, *J. Occup. Med. Toxicol.* **1**, 2006, 1–6.

[42]

L. Friberg and C.G. Elinder, WHO, Environmental Health Criteria, Geneva, 1992.

[43]

D. Beton, G. Andrews, H. Davies, L. Howells and G. Smith, *Br. J. Ind. Med.* **23**, 1966, 292–301.

[44]

G.F. Nordberg, B.A. Fowler and M. Nordberg, Handbook on the Toxicology of Metals, fourth ed., 2014, Academic Press, Elsevier/AP.

[45]

T.S. Nawrot, J.A. Staessen, H.A. Roels, E. Munters, A. Cuypers, T. Richart, A. Ruttens, K. Smeets, H. Clijsters and J. Vangronsveld, *Biometals* **23**, 2010, 769–782.

[46]

FAO/WHO (Food and Agriculture Organization/World Health Organization), Geneva, 2006.

[47]

Scientific opinion of the panel on contaminants in the food chain on a request from the European Commission on cadmium in food, *EFSA J.* **980**, 2009, 1–139.

[48]

P.G. Reeves and R.L. Chaney, *Sci. Total Environ.* **398**, 2008, 13–19.

[49]

Q. Zhai, A. Narbad and W. Chen, *Nutrients* **7**, 2015, 552–571.

[50]

W.L. Zhang, Y. Du, M.M. Zhai and Q. Shang, *Sci. Total Environ.* **470**, 2014, 224–228.

[51]

N.D. Minh, R.L. Hough, Y. Nyberg, N.C. Vinh, N.M. Khai and I. Öborn, *Sci. Total Environ.* **416**, 2012, 164–171.

[52]

A. Åkesson, P. Bjellerup, T. Lundh, J. Lidfeldt, C. Nerbrand, G. Samsioe, S. Skerfving and M. Vahter, *Environ. Health Perspect.* 2006, 830–834.

[53]

R. Schutte, T.S. Nawrot, T. Richart, L. Thijs, D. Vanderschueren, T. Kuznetsova, E. Van Hecke, H.A. Roels and J.A. Staessen, *Environ. Health Perspect.* **116**, 2008, 777–783.

[54]

M.H. Bhattacharyya, *Toxicol. Appl. Pharmacol.* **238**, 2009, 258–265.

[55]

L. Järup, M. Berglund, C.G. Elinder, G. Nordberg and M. Vanter, *Scand. J. Work Environ. Health* 1998, 1–51.

[56]

C.H. Wang, S. Brown and M.H. Bhattacharyya, *Toxicol. Appl. Pharmacol.* **127**, 1994, 320–330.

[57]

F. Forray and D. Hallbauer, *Environ. Geol.* **39**, 2000, 1372–1384.

[58]

G.F. Nordberg, K. Nogawa, M. Nordberg and L.T. Friberg, In: G. Nordberg, B. Fowler, M. Nordberg and L. Friberg, (Eds.), *Chap. 23 in Handbook on the Toxicology of Metals (Third Edition),* 2007, Academic Press, Elsevier.

[59]

M.B. Kirkham, *Geoderma* **137**, 2006, 19–32.

[60]

A. Oskarsson, A. Widell, M. Olsson and K.P. Grawé, *Biometals* **17**, 2004, 531–534.

[61]

E. Kurowska and W. Bal, *Adv. Mol. Toxicol.* **4**, 2010, 85–126.

[62]

P. Patnaik, A Comprehensive Guide to the Hazardous Properties of Chemical Substances, 2007, John Wiley & Sons.

[63]

M. Filipič, *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* **733**, 2012, 69–77.

[64]

M.J. Stillman, C.F. Shaw and K.T. Suzuki, Metallothionein: Synthesis, Structure, and Properties of Metallothioneins, Phytochelatins, and Metal-Thiolate Complexes, 1992, Wiley-VCH.

[65]

J. Liu, Y. Liu, S.S. Habeebu and C.D. Klaassen, *Toxicol. Sci.* **46**, 1998, 197–203.

[66]

C.D. Klaassen, J. Liu and B.A. Diwan, *Toxicol. Appl. Pharmacol.* **238**, 2009, 215–220.

[67]

A. Åkesson, L. Barregard, I.A. Bergdahl, G.F. Nordberg, M. Nordberg and S. Skerfving, *Environ. Health Perspect. (Online)* **122**, 2014, 431–438.

[68]

M. Akerstrom, L. Barregard, T. Lundh and G. Sallsten, *Toxicol. Appl. Pharmacol.* **268**, 2013, 286–293.

[69]

B. Amzal, B. Julin, M. Vahter, A. Wolk, G. Johanson and A. Akesson, *Environ. Health Perspect.* **117**, 2009, 1293–1301.

[70]

Y. Liang, L. Lei, J. Nilsson, H. Li, M. Nordberg, A. Bernard, G.F. Nordberg, I.A. Bergdahl and T. Jin, *Environ. Health Perspect.* **120**, 2012, 223–228.

[71]

M.S. Sinicropi, D. Amantea, A. Caruso and C. Saturnino, *Arch. Toxicol.* **84**, 2010, 501–520.

[72]

M. Stillman, W. Cai and A. Zelazowski, *J. Biol. Chem.* **262**, 1987, 4538–4548.

[73]

S. Jenkitkasemwong, C.Y. Wang, B. Mackenzie and M.D. Knutson, *Biometals* **25**, 2012, 643–655.

[74]

F. Thévenod, *Biometals* **23**, 2010, 857–875.

[75]

F. Thevenod and J.M. Friedmann, *FASEB J.* **13**, 1999, 1751–1761.

[76]

M.E. Figueiredo-Pereira, S. Yakushin and G. Cohen, *J. Biol. Chem.* **273**, 1998, 12703–12709.

[77]

H. Kozlowski, P. Kolkowska, J. Watly, K. Krzywoszynska and S. Potocki, *Curr. Med. Chem.* **21**, 2014, 3721–3740.

[78]

I. Sóvágó, K. Varnagy and A. Benyei, *Magyar Kémiai Folyóirat* **92**, 1986, 114–116.

[79]

G. Crisponi and M. Remelli, *Coord. Chem. Rev.* **252**, 2008, 1225–1240.

[80]

G. Borghesani, F. Pulidori, M. Remelli, R. Purrello and E. Rizzarelli, *J. Chem. Soc. Dalton Trans.* 1990, 2095–2100.

[81]

R.M. Smith and A.E. Martell, Critical Stability Constants, 1974–1989, Plenum Press; New York and London.

[82]

P.G. Daniele, P. Amico, G. Ostacoli and V. Zelano, *Anal. Chim.* **73**, 1983, 199–212.

[83]

I. Sovago, T. Kiss, A. Gergely, D.G. Tuck, O. Yamauchi, A.C.M. Bourg, A. Braibanti, R.H. Byrne, L.H.J. Lajunen, H.K.J. Powell, R.M. Byrne, J.R. Duffield, B. Holmberg, S. Ishiguro, T.A. Kaden, S.H. Laurie, R.B. Martin, P. Paoletti, R. Portanova, S. Sjoberg, C.B. Melios, M.P. Zhang, P. Valenta, M.T. Beck, P.K. Bhattacharya, M.C. Vaz, K.I. Popov, L.D. Pettit and G.R. Choppin, *Pure Appl. Chem.* **65**, 1993, 1029–1080.

[84]

G.N. Mukherjee and H.K. Sahu, *J. Indian Chem. Soc.* **75**, 1998, 143–147.

[85]

E. Farkas, A. Gergely and E. Kas, *J. Inorg. Nucl. Chem.* **43**, 1981, 1591–1597.

[86]

G.M. Barnard, T. Boddington, J.E. Gregor, L.D. Pettit and N. Taylor, *Talanta* **37**, 1990, 219–228.

[87]

F. Rey, J.M. Antelo, F. Arce and F.J. Penedo, *Polyhedron* **9**, 1990, 665–668.

[88]

R. Dodke and F. Khan, *J. Indian Chem. Soc.* **70**, 1993, 14–18.

[89]

J. Benzakour, G. Antonetti and G. Ferroni, *Bull. Soc. Chim. Belg.* **97**, 1988, 541–542.

[90]

A. Gergely, *Acta Chim. Acad. Sci. Hung.* **59**, 1969, 309–311.

[91]

C.W. Childs and D.D. Perrin, *J. Chem. Soc. A Inorg. Phys. Theor.* 1969, 1039–1044.

[92]

B.S. Sekhon, P.P. Singh and S.L. Chopra, *Indian J. Chem.* **9**, 1971, 485.

[93]

A. Albert, *Biochem. J.* **50**, 1952, 690–697.

[94]

G.R. Lenz and A.E. Martell, *Biochemistry* **3**, 1964, 745–750.

[95]

D.D. Perrin, *J. Chem. Soc. (Resumed)* 1959, 290–296.

[96]

D.R. Williams and P.A. Yeo, *J. Chem. Soc. Dalton Trans.* 1972, 1988–1990.

[97]

K.S. Rajan, S. Mainer and J.M. Davis, *Bioinorg. Chem.* **9**, 1978, 187–203.

[98]

A.C. Baxter and D.R. Williams, *J. Chem. Soc. Dalton Trans.* 1974, 1117–1120.

[99]

D.R. Williams, *J. Chem. Soc. Dalton Trans.* 1973, 1064–1066.

[100]

R. Gowda and M. Venkatappa, *J. Electrochem. Soc. India* **30**, 1981, 336.

[101]

D.R. Williams, *J. Chem. Soc. A Inorg. Phys. Theor.* 1970, 1550–1555.

[102]

D.D. Perrin and I.G. Sayce, *J. Chem. Soc. A Inorg. Phys. Theor.* 1968, 53–57.

[103]

H. Demirelli and F. Koseoglu, *J. Solut. Chem.* **34**, 2005, 561–577.

[104]

G. Brookes and L.D. Pettit, *J. Chem. Soc. Dalton Trans.* 1976, 42–46.

[105]

C. Conato, A. Contino, G. Maccarrone, A. Magri, M. Remelli and G. Tabbi, *Therm. Acta* **362**, 2000, 13–23.

[106]

C.F. Baes and R. Mesmer, The Hydrolysis of Cations, 1976, John Wiley and Sons; New York.

[107]

H. Irving and R. Williams, *J. Chem. Soc. (Resumed)* 1953, 3192–3210.

[108]

P.J. Barrie, A. Gyani, M. Motevalli and P. O'Brien, *Inorg. Chem.* **32**, 1993, 3862–3867.

[109]

R.J. Flook, H.C. Freeman, C.J. Moore and M.L. Scudder, *J. Chem. Soc. Chem. Commun.* 1973, 753–754.

[110]

X.X. Wang J, W.X. Ma, F.J. Yin, T. Guo, L.D. Lu, X.J. Yang and X. Wang, *J. Inorg. Organometal. Polym. Mater.* **19**, 2009, 401–409.

[111]

F. Fuess and H. Bartunik, *Acta Crystallogr. Sect. B Struct. Crystallogr. Cryst. Chem.* **32**, 1976, 2803–2806.

[112]

D. Perrin and I. Sayce, *J. Chem. Soc. A Inorg. Phys. Theor.* 1968, 53–57.

[113]

J.N. Rebilly, P.W. Gardner, G.R. Darling, J. Bacsa and M.J. Rosseinsky, *Inorg. Chem.* **47**, 2008, 9390–9399.

[114]

I. Sóvágó and K. Várnagy, Cadmium(II) complexes of amino acids and peptides, In: *Cadmium: From Toxicity to Essentiality,* 2013, Springer, 275–302.

[115]

V. Jószai, Z. Nagy, K. Ősz, D. Sanna, G. Di Natale, D. La Mendola, G. Pappalardo, E. Rizzarelli and I. Sóvágó, *J. Inorg. Biochem.* **100**, 2006, 1399–1409.

[116]

V. Guantieri, A. Venzo, V. Di Marco, M. Acampora and B. Biondi, *Inorg. Chim. Acta* **360**, 2007, 4051–4057.

[117]

P.G. Daniele, P. Amico and G. Ostacoli, *Inorg. Chim. Acta* **66**, 1982, 65–70.

[118]

G. Arena, V. Cucinotta, S. Musumeci, R. Purrello and E. Rizzarelli, *Anal. Chim.* **74**, 1984, 399–412.

[119]

S. Timári, C. Kállay, K. Ősz, I. Sóvágó and K. Várnagy, *Dalton Trans.* 2009, 1962–1971.

[120]

B.J. Scott and A. Bradwell, *Clin. Chem.* **29**, 1983, 629–633.

[121]

J.M. Berg and H.A. Godwin, *Annu. Rev. Biophys. Biomol. Struct.* **26**, 1997, 357–371.

[122]

F. Wang, F. Pierce, K. Ganapathy, B.B. Gump, J.A. MacKenzie, Y. Mechref and K.J. Bendinskas, *Chromatogr. B Anal. Technol. Biomed. Life Sci.* **934**, 2013, 26–33.

[123]

P.J. Sadler and J.H. Viles, *Inorg. Chem.* **35**, 1996, 4490–4496.

[124]

W. Bal, J. Christodoulou, P.J. Sadler and A. Tucker, *J. Inorg. Biochem.* **70**, 1998, 33–39.

[125]

A.J. Stewart, C.A. Blindauer, S. Berezenko, D. Sleep and P.J. Sadler, *Proc. Natl. Acad. Sci.* **100**, 2003, 3701–3706.

[126]

M. Sokołowska, M. Wszelaka-Rylik, J. Poznański and W. Bal, *J. Inorg. Biochem.* **103**, 2009, 1005–1013.

[127]

W. Bal, M. Sokołowska, E. Kurowska and P. Faller, *Biochim. Biophys. Acta (BBA) Gen. Subj.* **1830**, 2013, 5444–5455.

[128]

E.O. Martins and T. Drakenberg, *Inorg. Chim. Acta* **67**, 1982, 71–74.

[129]

W. Goumakos, J. Laussac and B. Sarkar, *Biochem. Cell Biol.* **69**, 1991, 809–820.

[130]

M. Chen, H. Guo, Y. Liu and Q. Zhang, *J. Biochem. Mol. Toxicol.* **28**, 2014, 281–287.

[131]

J. Liu, H. Liu, Y. Li and H. Wang, *J. Biol. Phys.* **40**, 2014, 313–323.

[132]

T.T. Morris, J.L. Keir, S.J. Boshart, V.P. Lobanov, A.M. Ruhland, N. Bahl and J. Gailer, *J. Chromatogr. B* **958**, 2014, 16–21.

[133]

H. Kozłowski, J. Urbańska, I. Sovago, K. Varnagy, A. Kiss, J. Spychała and K. Cherifi, *Polyhedron* **9**, 1990, 831–837.

[134]

K. Cherifi, B. Decock-Le Reverend, C. Loucheux, K. Varnagy, T. Kiss, I. Sovago and H. Kozlowski, *J. Inorg. Biochem.* **38**, 1990, 69–80.

[135]

A. Krezel and W. Bal, *Acta Biochim. Pol.* **46**, 1999, 567–580.

[136]

A.M. Corrie, M.D. Walker and D.R. Williams, *J. Chem. Soc. Dalton Trans.* 1976, 1012–1015.

[137]

D. Perrin and A.E. Watt, *Biochim. Biophys. Acta (BBA) Gen. Subj.* **230**, 1971, 96–104.

[138]

A.M. Carrie, M.D. Walker and D.R. Williams, *J. Chem. Soc. Dalton Trans.* 1976, 1012–1015.

[139]

B.J. Fuhr and D.L. Rabenstein, *J. Am. Chem. Soc.* **95**, 1973, 6944–6950.

[140]

K. Połeć-Pawlak, R. Ruzik and E. Lipiec, *Talanta* **72**, 2007, 1564–1572.

[141]

M. Belcastro, T. Marino, N. Russo and M. Toscano, *J. Inorg. Biochem.* **103**, 2009, 50–57.

[142]

O. Delalande, H. Desvaux, E. Godat, A. Valleix, C. Junot, J. Labarre and Y. Boulard, *FEBS J.* **277**, 2010, 5086–5096.

[143]

M. Glušič, P. Ropret, K. Vogel-Mikuš and J. Grdadolnik, *Acta Chim. Slov.* **60**, 2013, 61–69.

[144]

M. Glušič, J. Stare, J. Grdadolnik and R. Vianello, *J. Inorg. Biochem.* **119**, 2013, 90–94.

[145]

A. Corrie, M. Walker and D. Williams, *J. Chem. Soc. Dalton Trans.* 1976, 1012–1015.

[146]

J. Mendieta, M. Dıaz-Cruz, A. Monjonell, R. Tauler and M. Esteban, *Anal. Chim. Acta* **390**, 1999, 15–25.

[147]

M. Erk and B. Raspor, *J. Electroanal. Chem.* **502**, 2001, 174–179.

[148]

M. Díaz-Cruz, J. Díaz-Cruz and M. Esteban, *Electroanalysis* **14**, 2002, 899–905.

[149]

A. Muñoz, F. Laib, D.H. Petering and C.F. Shaw, III, *J. Biol. Inorg. Chem.* **4**, 1999, 495–507.

[150]

T.M. DeSilva, G. Veglia, F. Porcelli, A.M. Prantner and S.J. Opella, *Biopolymers* **64**, 2002, 189–197.

[151]

A. Jancsó, D. Szunyogh, F.H. Larsen, P.W. Thulstrup, N.J. Christensen, B. Gyurcsik and L. Hemmingsen, *Metallomics* **3**, 2011, 1331–1339.

[152]

A. Jancsó, B. Gyurcsik, E. Mesterházy and R. Berkecz, *J. Inorg. Biochem.* **126**, 2013, 96–103.

[153]

K. Krzywoszynska, M. Rowinska-Zyrek, D. Witkowska, S. Potocki, M. Luczkowski and H. Kozlowski, *Dalton Trans.* **40**, 2011, 10434–10439.

[154]

K. Krzywoszynska and H. Kozlowski, *Dalton Trans.* **43**, 2014, 16207–16212.

[155]

S. Potocki, M. Rowinska-Zyrek, D. Valensin, K. Krzywoszynska, D. Witkowska, M. Luczkowski and H. Kozlowski, *Inorg. Chem.* **50**, 2011, 6135–6145.

[156]

N. Lihi, Á. Grenács, S. Timári, I. Turi, I. Bányai, I. Sóvágó and K. Várnagy, *New J. Chem.* **39**, 2015, 8364–8372.

[157]

X. Chen, M. Chu and D.P. Giedroc, *J. Biol. Inorg. Chem.* **5**, 2000, 93–101.

[158]

O.I. Leszczyszyn, C.R.J. White and C.A. Blindauer, *Mol. BioSyst.* **6**, 2010, 1592–1603.

[159]

C.A. Blindauer, *J. Inorg. Biochem.* **102**, 2008, 507–521.

[160]

N. Romero-Isart, N. Duran, M. Capdevila, P. Gonzalez-Duarte, S. Maspoch and J. Torres, *Inorg. Chim. Acta* **278**, 1998, 10–14.

[161]

W. Xia, H. Li, K.H. Sze and H. Sun, *J. Am. Chem. Soc.* **131**, 2009, 10031–10040.

[162]

M. Rowinska-Zyrek, D. Witkowska, S. Bielinska, W. Kamysz and H. Kozlowski, *Dalton Trans.* **40**, 2011, 5604–5610.

[163]

M. Rowinska-Zyrek, S. Potocki, D. Witkowska, D. Valensin and H. Kozlowski, *Dalton Trans.* **42**, 2013, 6012–6020.

[164]

P. Kolkowska, K. Krzywoszynska, S. Potocki, P.R. Chetana, M. Spodzieja, S. Rodziewicz-Motowidlo and H. Kozlowski, *Dalton Trans.* **44**, 2015, 9887–9900.

[165]

A.F. Peacock and V.L. Pecoraro, Natural and artificial proteins containing cadmium, In: *Cadmium: From Toxicity to Essentiality,* 2013, Springer, 303–337.

[166]

E. Andresen and H. Küpper, Cadmium toxicity in plants, In: *Cadmium: From Toxicity to Essentiality,* 2013, Springer, 395–413.

[167]

E. Freisinger and M. Vašák, Cadmium in metallothioneins, In: *Cadmium: From Toxicity to Essentiality,* 2013, Springer, 339–371.

[168]

H. Gil, E. Kang, K. Lee, J. Yang, E. Lee and S. Hong, *Hum. Exp. Toxicol.* **30**, 2011, 79–83.

[169]

Y. Cao, A. Chen, M. Bottai, K.L. Caldwell and W.J. Rogan, *J. Pediatr.* **163**, 2013, 598–600.

[170]

M. Blanusa, V.M. Varnai, M. Piasek and K. Kostial, *Curr. Med. Chem.* **12**, 2005, 2771–2794.

[171]

O. Andersen, Chapter 5, In: G.C.J. Aaseth, G. Crisponi and O. Andersen, (Eds.), *Chelation Therapy in the Treatment of Metal Intoxication,* 2016, Academic Press.

[172]

V.M. Nurchi, M. Crespo-Alonso, L. Toso, J. Izabela Lachowicz and G. Crisponi, *Mini Rev. Med. Chem.* **13**, 2013, 1541–1549.

[173]

L.R. Cantilena and C.D. Klaassen, *Toxicol. Appl. Pharmacol.* **63**, 1982, 173–180.

[174]

T. Dalhamn and L. Friberg, *Acta Pharmacol. Toxicol.* **11**, 1955, 68–71.

[175]

M. Jones, A. Weaver and W. Weller, *Res. Commun. Chem. Pathol. Pharmacol.* **22**, 1978, 581–588.

[176]

M.A. Basinger, M.M. Jones and L.A. Shinobu, *J. Inorg. Nucl. Chem.* **43**, 1981, 3039–3042.

[177]

L.R. Cantilena and C.D. Klaassen, *Toxicol. Appl. Pharmacol.* **58**, 1981, 452–460.

[178]

V. Eybl, J. Sýkora and F. Mertl, *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* **252**, 1965, 85–93.

[179]

G.S. Ding and Y.Y. Liang, *J. Appl. Toxicol.* **11**, 1991, 7–14.

[180]

O. Andersen and P. Grandjean, *Pharmacol. Toxicol.* **64**, 1989, 210–215.

[181]

O. Andersen and J.B. Nielsen, *Toxicology* **55**, 1989, 1–14.

[182]

O. Andersen, J.B. Nielsen and P. Svendsen, *Toxicology* **48**, 1988, 225–236.

[183]

M.M. Sarić, M. Blanuša, D. Jureša, M. Šarić, V.M. Varnai and K. Kostial, *Basic Clin. Pharmacol. Toxicol.* **94**, 2004, 119–123.

[184]

M.M. Jones, P.K. Singh, G.R. Gale, A.B. Smith and L.M. Atkins, *Pharmacol. Toxicol.* **70**, 1992, 336–343.

[185]

M.M. Jones, P.K. Singh, M.A. Basinger, G.R. Gale, A.B. Smith and W.R. Harris, *Chem. Res. Toxicol.* **7**, 1994, 367–373.

[186]

P.K. Singh, M.M. Jones, K. Kostial, M. Blanuša, M. Piasek and N. Restek-Samarzija, *Chem. Res. Toxicol.* **9**, 1996, 965–969.

[187]

Z.A. Shaikh and O.J. Lucis, *Arch. Environ. Health Int. J.* **24**, 1972, 410–418.

[188]

M.G. Cherian, *J. Toxicol. Environ. Health Part A Curr. Issues* **6**, 1980, 393–401.

[189]

A.S. Saljooghi and S.J.A. Fatemi, *Biometals* **23**, 2010, 707–712.

[190]

S.J. Fatemi, A.S. Saljooghi, F.D. Balooch, M. Iranmanesh and M.R. Golbafan, *Toxicol. Ind. Health* 2011, 1–7.

[191]

P. Butaye, L.A. Devriese and F. Haesebrouck, *Clin. Microbiol. Rev.* **16**, 2003, 175–188.

[192]

J. Ivanova, Y.G. Gluhcheva, K. Kamenova, S. Arpadjan and M. Mitewa, *J. Trace Elem. Med Biol.* **26**, 2012, 279–284.

[193]

J. Ivanova, I. Pantcheva, M. Mitewa, S. Simova, H. Mayer-Figge and W. Sheldrick, *Open Chem.* **8**, 2010, 852–860.

[194]

X. Tang, J. Zhu, Z. Zhong, M. Luo, G. Li, Z. Gong, C. Zhang, F. Fei, X. Ruan and J. Zhou, *Toxicol. Appl. Pharmacol.* **305**, 2016, 143–152.

[195]

G. Crisponi, J. Aaseth and O. Andersen, Chapter 8, In: J. Aaseth, G. Crisponi and O. Andersen, (Eds.), *Chelation Therapy in the Treatment of Metal Intoxication,* 2016, Academic Press.

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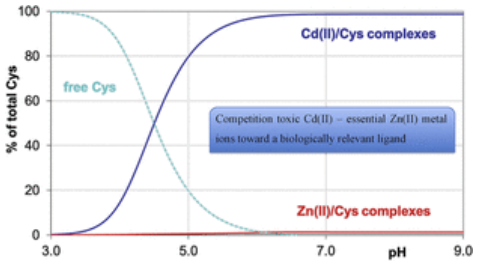

Highlights

- Mechanisms of cadmium toxicity in humans.
- Complex-formation equilibria of Cd(II) with amino acids and peptides.
- Competition Cd(II) – bivalent metal ions toward biologically relevant ligands.
- Chelation therapy for the treatment of Cd(II) toxicity.

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