

Review

The First-Row Transition Metals in the Periodic Table of Medicine

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Abstract: In this manuscript, we describe medical applications of each first-row transition metal including nutritional, pharmaceutical, and diagnostic applications. The 10 first-row transition metals in particular are found to have many applications since there five essential elements among them. We summarize the aqueous chemistry of each element to illustrate that these fundamental properties are linked to medical applications and will dictate some of nature's solutions to the needs of cells. The five essential trace elements—iron, copper, zinc, manganese, and cobalt—represent four redox active elements and one redox inactive element. Since electron transfer is a critical process that must happen for life, it is therefore not surprising that four of the essential trace elements are involved in such processes, whereas the one non-redox active element is found to have important roles as a secondary messenger.. Perhaps surprising is the fact that scandium, titanium, vanadium, chromium, and nickel have many applications, covering the entire range of benefits including controlling pathogen growth, pharmaceutical and diagnostic applications, including benefits such as nutritional additives and hardware production of key medical devices. Some patterns emerge in the summary of biological function and medical roles that can be attributed to small differences in the first-row transition metals.

Keywords: first-row transition metals; metals in medicine; periodic table; speciation

1. Introduction

Cations are counter ions in biology and critical for maintaining charge balance. Proteins, DNA, and RNA contain charged residues where counter ions are important to the specific three-dimensional structure and function of each [1]. Metal cations that neutralize these charges include main group metal ions and transition metals ions. Transition metal ions are generally less commonly found in nature compared to the alkali metal ions, such as sodium and potassium ions, and the alkaline earth metal ions, such as magnesium and calcium ions. However, they do play a critical role, whether it be structural or catalytic [2]. In the following manuscript, we summarize the medicinal properties of the first-row transition metals and include a comparison of the different metal ions and their speciation. Because medical applications often rely on the roles of the elements in biology, we also included some brief summaries and a discussion of the occurrences of the first-row elements. Indeed, the use of each metal ion as counterions plays an important role for the medical applications, and by summarizing the speciation of each of these metals ions, the reader will recognize the properties that are important to the action and applications of each element. To summarize the applications of the first-row transition metals, a medicinal periodic table of the elements is presented (Figure 1). Details of the medicinal applications of all the elements within the periodic table are shown in this figure and the particulars are identified in the caption. However, in this manuscript we focused

on the pharmaceutical, diagnostic, and other medicinal applications of the first-row transition metals in the periodic table.

The year 2019 is designated by the United Nations as the International Year of the Periodic Table in celebration of the first report of the periodic table in 1869 by Dmitri Mendeleev of Russia. There were many key discoveries that led to the organization of the elements in the manner we recognize today, examples of which have been highlighted elsewhere [3,4]. A total of six scientists worked on the periodic table around the same time, though only two are well known [5]. In addition to Mendeleev's periodic table, Julius Lothar Meyer of Germany continued his earlier work and reported a periodic table in 1870. As elegantly articulated by Eric R. Scerri [5], "the periodic table of the elements is one of the most powerful icons in science: a single document that captures the essence of chemistry in an elegant pattern. Nothing like it exists in biology or physics or any other branch of science". Although both periodic tables properly describe the succession of the first-row metals, only Mendeleev's periodic table has the changes in properties consistent with the medicinal applications summarized in this manuscript. We have generated a periodic table of medicines shown in Figure 1, of which nutritional, pharmaceutical, and diagnostic applications as well as roles in medicinal hardware of first-row transition metals are a small part.

Metal ions have important catalytic and structural roles in biology. One-third of the proteins in the human genome contain a metal ion that plays a key role as a cofactor. For example, iron (abbreviated Fe from the Latin *ferrum*) is an important ion for the proteins involved in respiration and electron transport [6]. This means that this metal ion, found in oxidation states II and III, will coordinate to a protein and play an either structural or catalytic role. Each of the first-row transition elements have medical applications, many of which are components of materials used in medical procedures as well as roles as pharmaceuticals or diagnostic agents. Application of metal-based drugs are different from carbon-based drugs, because upon processing, the carbon-based drugs generally break down into CO₂ and various metabolites. Metal-based drugs will metabolise and form a simple metal ion which will interact with cellular components and form new compounds. Such new compounds may have a biological effect and, thus, extend the effects of the original drug added to the system. In this work, we briefly summarized the medical applications, followed by a section on speciation of metal ions highlighting the metal ions that form at neutral physiological pH for each element. Although other conditions exist in nature in the biosphere, such as the acidic environment of the stomach or in bacteria, fungi, and algae, we here focus on the metal ions forming near neutral pH in cells and the blood. The images shown in the periodic table of medicines (Figure 1) not only demonstrate the versatile uses of the first-row transition metals but illustrate the fact that nearly all elements of the periodic table have some direct medicinal use.

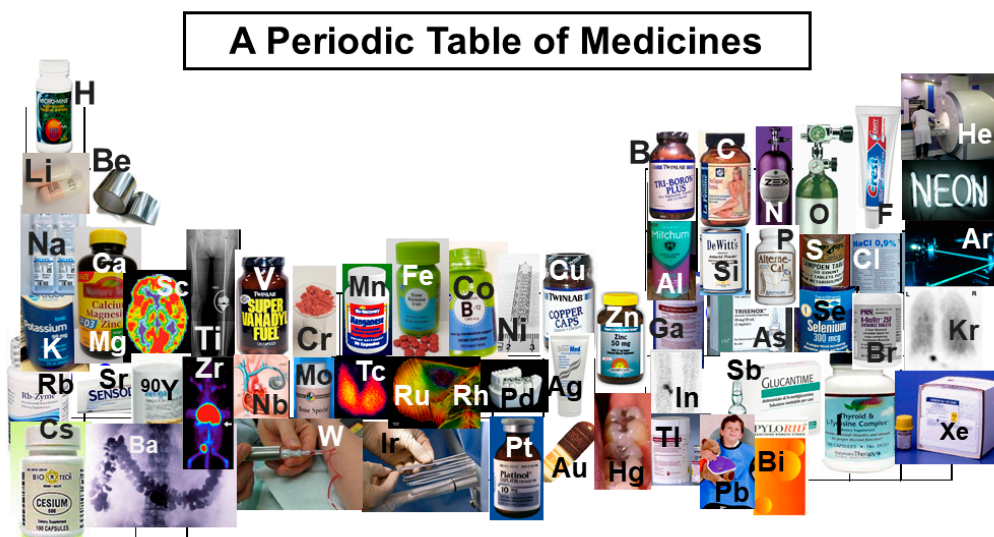


Figure 1. The periodic table with known medicinal uses of each main group or transition metal element when available. In the following, we list the use of each element. Hydrogen (H), boron (B), carbon (C), calcium (Ca), phosphorous (P), potassium (K), magnesium (Mg), vanadium (V), manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), selenium (Se), rubidium (Ru), molybdenum (Mo), and cesium (Cs) are commonly found in supplements readily available to the public and are illustrated as such. Helium (He) is crucial in the operation of MRI machines. Lithium (Li) as lithium carbonate is the most common treatment of bipolar disorder. Beryllium (Be) foil is used as shielding in radiographic instruments. Nitrogen (N), as nitrous oxide, is a common anesthetic. Oxygen (O) has many medical uses, including anesthetics and resuscitation, and is illustrated here for use in ventilation. Fluorine (F) and tin (Sn) as stannous fluoride are a common ingredient in toothpaste. Sodium (Na) and chlorine (Cl) are used as NaCl in saline solutions. Aluminum (Al) compounds are a common active ingredient in antiperspirant deodorants. Silicon (Si) is used in antacid products. Sulfur (S) is illustrated as campden tablets, which are used for sterilization in beer fermentation. Argon (Ar) lasers are used in eye surgery. Zirconium (Zr) is used in immuno-positron emission tomography (PET) imaging while scandium (Sc) is a candidate for the same technique. Titanium (Ti), palladium (Pd), niobium (Nb), nickel (Ni), and tantalum (Ta) are used in medical implants. Chromium (Cr) is shown as Cr(III) picolinate, which is a controversial supplement used in lowering insulin resistance. Gallium (Ga), yttrium (Y), technetium (Tc), lanthanum (La), astatine (At), and actinium (Ac) are all used in nuclear medicine. Arsenic (As), as As(III) trioxide, is used to treat certain forms of leukemia. Bromine (Br) as KBr is an active ingredient in canine seizure medication. Krypton (Kr) was used in lung ventilation studies but has since been phased out. Strontium (Sr) is used in Sensodyne® toothpaste. Rhodium (Rh), ruthenium (Ru), and rhenium (Re) complexes are used as anticancer agents. Silver (Ag) is used in antibacterial ointments. Indium (In) is used in white blood cell scans. Antimony (Sb) is used in leishmania medicine. Barium (Ba) is used in X-ray imaging of the gastrointestinal tract. Tungsten (W) is used in shielded syringes. Iridium (Ir) is used in brachytherapy. Gold (Au) was used as a treatment for rheumatoid arthritis but has been phased out. Mercury (Hg) is used in dental amalgams. Lead (Pb) is used in X-ray aprons. Bismuth (Bi) is used in stomach ulcer medicine. Neon (Ne), germanium (Ge), cadmium (Cd), tellurium (Tl), hafnium (Hf), osmium (Os), polonium (Po), francium (Fr), radon (Rn), and radium (Ra) although most of these are toxic elements for human life, some of these elements are under development as potential agents for disease treatment but to our knowledge they are not currently used for beneficial applications in medicine. References to most of these facts are dispersed throughout the manuscript.

Several first-row transition metals, including the elements iron, copper, zinc, manganese, and cobalt, are essential elements for humans. The simplest definition of an essential element is that the element is required for life and its absence will result in the organisms death and/or severe malfunction [7]. However, in addition to mammals the biosphere includes many organisms for which additional metal ions are critical for growth and development [8–10]. It is important to emphasize that an element's essentiality can vary depending on whether the focus is for humans or other organisms. For example, an element such as nickel is essential for the bacterial enzyme urease that is an essential component for bacteria but not for human beings. This means that nickel is required for bacteria and needed for their growth, but since such metabolic pathways are not found in human beings, it is not essential for human beings. Experiments addressing essentiality are very difficult to conduct particularly with elements such as the first-row transition metals, because materials containing the metal ions are very similar and most metals preparations will contain trace levels of the related elements. For examples, iron supplements will contain trace levels of cobalt, manganese, nickel, and vanadium. Thus, the question of the essentiality of vanadium will be difficult to address experimentally because vanadium will be administered with the iron in supplements and food. Consequently, a number of controversies exist with regard to chromium and whether it is essential or not.

The human body consists mainly (96%) of four elements, carbon (C), oxygen (O), hydrogen (H), and nitrogen (N). The rest of the elements make up 4% and that includes all the first-row transition metal ions as well as the rest of the periodic table. Scandium is present in very low to non-existent concentrations in humans and the biosphere, but it is more plentiful in the Earth's crust even though

its minerals are rare and it is considered a rare-earth element. In contrast, iron is considered a trace element in the human body despite being the most plentiful of the first-row transition metals in the Earth's crust (see Figure 2) [11]. Summarizing the most common minerals in which the first-row transition elements occur in the environment is important for the technological development of the applications of these elements. Table 1 lists these minerals, which are also referred to as oxides and sulfides. Each first-row transition element lends different colors to their respective minerals, the diversity of which is demonstrated, as described in Table 1. Although most of these minerals are not very soluble in water, they can leech into groundwater with rainfall. As a result, the metal ions are transported to the water supply and end up being distributed to human beings. Most countries have government agencies, such as the Environmental Protection Agency in the United States, that have stringent regulations on the allowable concentrations of these metals in drinking water because while many of these metals are largely considered non-toxic, overload of any element in the human body can lead to undesirable health effects.

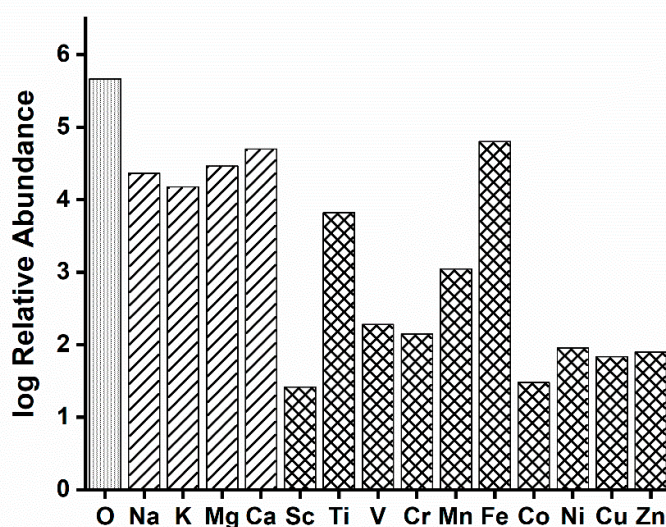


Figure 2. The relative abundance (ppm) on a log scale of oxygen (small dashes), biologically relevant main group metals (diagonal lines), and the first-row transition metals (cross hatching) in the Earth's crust on a log scale. This figure was redrawn and modified from Reference [12].

It is generally recognized that some metal ions are necessary for life but that too much of the metal can be problematic and lead to disease. It therefore seems obvious that the addition of some compounds containing essential metals will, in some cases, benefit organisms. However, the ability of some metal ions to be involved in the formation of reactive oxygen species (ROS) underlines the need for systemic control. Uptake and excretion of metal ions are biological processes that are increasingly important in medicine, and the formulation of metal ions for supplements and therapeutic purposes are two conditions appreciated as important for human health. Drug delivery has also received recent consideration as an important facet of health. For example, the form of Fe in Fe-containing supplements matters given that uptake of iron citrate salts differs from iron chloride salts since uptake of Fe in citrate salts are more effective than that of Fe in chloride salts. Medicinal effects of any therapeutic agent is therefore a complex matter in which the delivery, uptake, biodistribution, and mode of action all play a role. In the following, we focused on summarizing the information on each first-row transition element and their activities and applications in biological systems and medicine.

Table 1. Common minerals of first-row transition metals.

Element	Common Minerals	Mineral Crystal System	Mineral Color	References
Scandium (Sc)	Thortveitite ($\text{Sc}_2\text{Si}_2\text{O}_7$)	Monoclinic	Grayish green	[13–16]
Titanium (Ti)	Ilmenite (FeTiO_3) rutile (TiO_2)	Hexagonal; tetragonal	Iron black; reddish brown	[11,12,15]
Vanadium (V)	Vanadinite [$\text{Pb}_5(\text{VO}_4)_3\text{Cl}$] carnotite [$\text{K}(\text{UO}_2)\text{VO}_4 \cdot 1.5 \text{H}_2\text{O}$]	Hexagonal; monoclinic	Red to brownish yellow; bright yellow to dark yellow	[11,12,15]
Chromium (Cr)	Chromite (FeCr_2O_4)	Cubic	Black	[11,12,15]
Manganese (Mn)	Pyrolusite (MnO_2)	Tetragonal	Black or dark grey	[12,15,17]
Iron (Fe)	Hematite, (Fe_2O_3) magnetite (Fe_3O_4)	Hexagonal; cubic	Red or black; iron black	[11,12,15]
Cobalt (Co)	Smaltite (CoAs_2) cobaltite (CoAsS) linnaetite (Co_3S_4)	All cubic	Grey to white; white to grey with purple tint; light gray to dark grey	[11,12,15]
Nickel (Ni)	Garnierite [$(\text{Ni},\text{Mg})_6\text{Si}_4\text{O}_{10}(\text{OH})_8$] pentlandite [$(\text{Ni},\text{Fe})_9\text{S}_8$]	N/A; cubic	N/A; bronze yellow	[11,12,15]
Copper (Cu)	Native metal, chalcocite (Cu_2S) chalcocite (Cu_2S)	Cubic; tetragonal; orthorhombic	Pale rose to copper red; brass yellow; blackish grey to black	[12,15]
Zinc (Zn)	Sphalerite (ZnS) smithsonite (ZnCO_3)	Cubic; hexagonal	Various colors possible	[11,12,15]

2. Properties of First-Row Transition Metals

The International Union of Pure and Applied Chemistry (IUPAC) definition of a transition metal is “an element whose atom has a partially filled d-subshell or which can give rise to cations with an incomplete d-subshell” [18]. Cotton and Wilkinson [11] expanded the IUPAC definition by including scandium and yttrium in group 3 as first- and second-row transition metals, respectively. The first transition metal, element 21—scandium, has an electronic configuration of $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^1$ (also described as an argon core with 4s filled and one electron in the 3d subshell, $[\text{Ar}]4s^2 3d^1$) and the last first-row transition metal, element 30—zinc, has the electronic configuration of $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10}$. Few of these metals exist in nature in their native metallic state. In general, they are found as metal ion complexes in the form of minerals, a number of which are listed in Table 1. The properties of these metal ions vary dramatically as illustrated in Figure 3a,b. In Figure 3a, the difference between the oxidation state of the blue vanadium(IV), vanadyl sulfate, and the white (colorless) vanadium(V), potassium metavanadate is visibly shown. Also, Figure 3b presents the metal chloride salts of Cr, Mn, Fe, Co, Ni, Cu, and Zn, in that order, where the variation in color from dark green to white demonstrates the differences in these systems even when the same anion is being compared. These changes originate in the systematic succession of completing the d-shell in the first-row-transition metal series and the consequence of this is described in many text books [11–13].

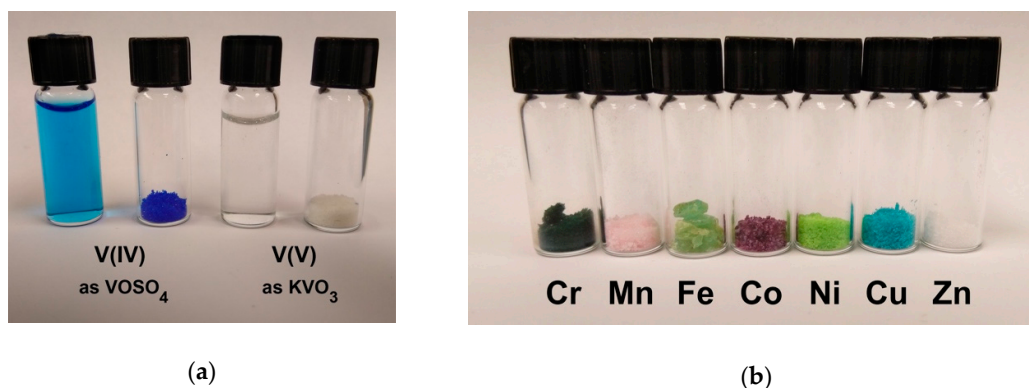


Figure 3. Demonstration of the diversity of metal chemistry. (a) Oxidation state affects chemistry, as V(IV) is a blue solution and solid, while V(V) is a colorless solution and white powder; (b) chloride salts of the first-row transition metals have different colors. Shown are mainly the oxidation state (II) and (III) metal complexes CrCl₃, MnCl₂, FeCl₃, CoCl₂, NiCl₂, CuCl₂, and ZnCl₂ with varying amounts of hydration.

Depending on the group number and the nature of the ligand and redox environments, the first-row transition metals can exist in several oxidation states [19]. Table 2 summarizes the possible oxidation states of the first-row transition metals as well as the most common oxidation state(s) under physiological conditions. The conditions suitable for most living matter consequently limits the chemistry exerted by the metal ions. The structure of metal ion complexes depends on whether the material is in the solid state or dissolved in solution. Under physiological conditions, the most common form of the first-row transition metals are oxidation states II or III, or in the case of vanadium (V), IV and V, and IV for titanium. Vanadium, in particular, tends to form oxides, being found in the oxidation state IV as the hydrated form of $V = O^{2+}$, and for oxidation state V, it is found in the form of VO_2^+ at low pH, as a coordination complex, or in the form of $H_2VO_4^-$ at neutral or basic pH. The structures of the hydrated cations vary; however, they all include octahedral geometries. Some metals, such as titanium, vanadium, copper, and zinc, can have stable four- and five-coordinate geometries, whereas most of the others tend to be six-coordinate [10]. There is a wide range of reactivity depending on the electronic composition, but there are some generalizations. For example, low oxidation state metal ions prefer to coordinate to nitrogen-based ligands, whereas higher oxidation states prefer to coordinate to oxygen-based ligands. This preference is very important, particularly with regards to the chemistry that each of these metals can undergo in physiological conditions. The properties of these are very different, as evidenced by the different aspect and color of the metal chloride salts shown in Figure 3.

In the following, we will first summarize the aqueous speciation chemistry of each first-row transition metal complex and then briefly describe the discovery, occurrence, and detailed physical properties of each element as we discuss each element separately. If relevant, we then summarize the biological roles of each element, followed by a description of their medical applications.

Table 2. Possible oxidation states and likely oxidation states in blood at pH 7.4 and under other biological conditions of first-row transition metals, where oxidation states in parentheses indicate rare but possible states.

Element	Possible Oxidation States	Oxidation States at pH 7.4 in Blood	Other Possible Oxidation States in the Biosphere	Reference(s)
Scandium (Sc)	III	III	III	[11,12,16]
Titanium (Ti)	0, II, III, IV	IV	0, III, IV	[11,12]
Vanadium (V)	−II, −I, I, II, III, IV, V	IV, V as metal oxides	III, IV, V	[11,12]
Chromium (Cr)	−IV, −II, −I, 0, I, II, III, V, VI	III	III, (IV), V, VI	[11,12,20]
Manganese (Mn)	−III, −II, −I, 0, I, II, III, V, VI, VII	II, IV, VII	II, III, IV, VII	[11,12]
Iron (Fe)	−II, 0, I, II, III, IV, V, VI	II, III	II, III, (IV)	[11,12,21]
Cobalt (Co)	−I, 0, I, II, III, IV	II, III	II, III	[11,12]
Nickel (Ni)	0, I, II, III, IV	I, II, III	0, II	[11,12]
Copper (Cu)	(0), I, II, III, (IV)	Mainly II	I, II	[11,12]
Zinc (Zn)	(I), II	II	II	[11,12]

3. Speciation of First-Row Transition Metal Ions in Aqueous Solutions

Because bodily fluids are responsible for the distribution of nutrients and drugs, it is important to know the form that the first-row transition metal ions exist in solution. Although some applications of the first-row transition metals are not based on their aqueous chemistry, there is no doubt that the speciation chemistry is important for the metal–protein, metal–DNA, metal–RNA or metal–metabolite complexation reactions that occur under physiological conditions.

Many first-row transition metals form divalent cations (oxidation state II) as one of the major oxidation states in blood and in the biosphere, as summarized in Table 2. However, Sc and Cr prefer oxidation state III, and Ti prefers oxidation state IV at pH 7.4. Vanadium prefers oxidation IV and V but forms metal oxides VO^{2+} and VO_2^+ . Oxidation state V of V also forms anionic species such as H_2VO_4^- at pH 7.4. Most of the transition metal ions undergo pH-dependent hydrolysis in aqueous solution and, thus, the concentration of a particular cation may be significantly reduced depending on the overall concentration. The properties of each metal ion are related to crystal field theory and ligand field stabilization resulting in the description of speciation chemistry. The following summary is taken from speciation diagrams in the book by Baes and Mesmer [21] and serves to illustrate the nature of the aqueous solutions of each first-row transition metal ions.

Scandium forms mononuclear ($\text{Sc}(\text{OH})^+$), dinuclear ($\text{Sc}_2(\text{OH})_2^{4+}$), or trinuclear ($\text{Sc}_3(\text{OH})_5^{4+}$) species in aqueous solution depending on pH and Sc concentration: these multinuclear species form at high concentration (0.1 M), whereas at 10 μM concentration there are very few dinuclear or trinuclear species. Titanium mainly forms cations in oxidation state II and IV, although some in oxidation state III can also form. Ti^{2+} forms at low pH and low redox potential and Ti in oxidation state IV is the major oxidation state forming several species depending on pH: $\text{Ti}(\text{OH})_3^+$, $\text{Ti}(\text{OH})_4$ and TiO_2 . Titanium in oxidation state III forms $\text{Ti}(\text{OH})_2^+$ and a dinuclear species $\text{Ti}_2(\text{OH})_2^{4+}$.

Vanadium is mainly present in the form of V(IV) and V(V). Both these ions form oxo species for V(IV), it is the vanadyl cation, VO^{2+} , and for V(V) the main species at low concentration and neutral pH is H_2VO_4^- , also referred to as vanadate. However, neither VO^{2+} or H_2VO_4^- forms in high concentration near neutral pH, because both these species form oligomeric species. For V(IV), the species VOOH^+ and $(\text{VOOH})_2^{2+}$ and polymeric species forms. For V(V) the polymeric species are $\text{V}_2\text{O}_7^{4-}$, $\text{V}_4\text{O}_{12}^{4-}$, and $\text{V}_5\text{O}_{15}^{5-}$ and other corresponding species in different protonation states. Thus, at neutral pH and at mM concentrations there is very little of the mononuclear species in solution. However, at basic pH, the speciation will be very different. Recently, it was discovered that V(III) is much more stable than anticipated, and it was found to form in aqueous solution by the reduction

with ascorbate [22]. The fact that this form of V was previously missed under physiological conditions is because some of the V(III) species are only observable using high-frequency and high-field EPR spectroscopy. Chromium exists in oxidation states II, III, and VI. Oxidation state II is reactive at various pH values and will react with water. Oxidation state III is stable under most physiological conditions forming the $\text{Cr}(\text{OH})^{2+}$, $\text{Cr}(\text{OH})_2^+$, $\text{Cr}(\text{OH})_4^-$, and probably $\text{Cr}(\text{OH})_3$. Even at μM concentration, oligomeric or polymolecular species form, including $\text{Cr}_2(\text{OH})_2^{4+}$ and $\text{Cr}_3(\text{OH})_4^{5+}$, so the specific species depends on the pH and the concentration. Oxidation state VI is toxic, forming HCrO_4^- , and above 10 mM, $\text{Cr}_2\text{O}_7^{2-}$.

Manganese exists in most different oxidation states, but only oxidation state II, III, and VII form in significant amounts in solution. Mn^{2+} hydrolyzes at pH 8 at 0.1 M concentration and the dinuclear species $\text{Mn}_2(\text{OH})_3^+$ forms. At 10 μM , Mn^{2+} exists up until pH 10, at which point $\text{Mn}(\text{OH})^+$ and the dinuclear species $\text{Mn}_2(\text{OH})_3^+$ form. Iron in oxidation state II and III form over a wide potential and pH range. The octahedral ferric iron (Fe(III)) complexes such as the purple hexa-aquo ion begin to hydrolyze at about pH 1 forming first the yellow $\text{Fe}(\text{H}_2\text{O})_5\text{OH}^{2+}$. At 10 μM , monomeric species form including $\text{Fe}(\text{H}_2\text{O})_4(\text{OH})_2^+$, $\text{Fe}(\text{H}_2\text{O})_3(\text{OH})_3^-$, and $\text{Fe}(\text{H}_2\text{O})_2(\text{OH})_4^-$. At 0.1 M, in addition to the $\text{Fe}(\text{H}_2\text{O})_5\text{OH}^{2+}$, polynuclear species form beginning with $\text{Fe}_2(\text{OH})_2^{4+}$, $\text{Fe}_3(\text{OH})_4^{5+}$, $\text{Fe}(\text{OH})_2^+$, $\text{Fe}(\text{OH})_3$, and $\text{Fe}(\text{OH})_4^-$. In contrast, the high spin ferrous hexa-aquo $\text{Fe}(\text{H}_2\text{O})_6^{2+}$ is stable up until about pH 10 at which point the $\text{Fe}(\text{OH})^+$, $\text{Fe}(\text{OH})_2$, and $\text{Fe}(\text{OH})_3^-$ species form.

Cobalt, in aqueous solutions, exists in the form of a cobaltous ion (Co^{2+}) because Co^{3+} is a powerful oxidizing agent which decomposes water. Co^{2+} is d^7 and ligand field stabilization energies disfavor the tetrahedral configuration compared to the octahedral configuration and, therefore, conditions exist in which both species are present in solution as $\text{Co}(\text{H}_2\text{O})_6^{2+}$ and $\text{Co}(\text{H}_2\text{O})_4^{2+}$. Speciation of Co^{2+} at 0.1 M results in Co^{2+} until about pH 8 when $\text{Co}_4(\text{OH})_4^{4+}$, $\text{Co}(\text{OH})_2$, and $\text{Co}(\text{OH})_3^-$ form. At low concentration, the speciation of Co^{2+} at 10 μM results in Co^{2+} until about pH 9.5 when $\text{Co}(\text{OH})^+$, $\text{Co}(\text{OH})_2$, and $\text{Co}(\text{OH})_3^-$ form. For Ni^{2+} , the major hydrolysis product is $\text{Ni}(\text{OH})^+$. At high concentration (0.1 M), a tetranuclear species ($\text{Ni}_4(\text{OH})_4^{4+}$) is formed at pH 7.5 just prior to the precipitation of $\text{Ni}(\text{OH})_2$ and formation of $\text{Ni}(\text{OH})_3^-$. At 10 μM , concentrations of Ni^{2+} exist until about pH 9.5 when $\text{Ni}(\text{OH})_2$, $\text{Ni}(\text{OH})_3^-$, and $\text{Ni}(\text{OH})_4^{2-}$ form.

Solutions of Cu^+ hydrolyze to form Cu_2O , which is insoluble. Cu^{2+} hydrolyzes at 0.1 M concentrations, forming $\text{Cu}_2(\text{OH})_2^{2+}$ before precipitation at pH 6. At pH 10, the mononuclear species forms $\text{Cu}(\text{OH})_2^0$, $\text{Cu}(\text{OH})_3^-$, and $\text{Cu}(\text{OH})_4^{2-}$. For speciation at 10 μM concentrations, Cu^{2+} exists until about pH 8.0, at which point $\text{Cu}_2(\text{OH})_2^{2+}$, $\text{Cu}(\text{OH})^+$, $\text{Cu}(\text{OH})_2^0$, $\text{Cu}(\text{OH})_3^-$, and $\text{Cu}(\text{OH})_4^{2-}$ form. The major form of Zn is the divalent Zn(II) ion, and little hydrolysis is observed in solution to about pH 8.5. At that point, $\text{Zn}(\text{OH})_2$ forms and above pH 11 $\text{Zn}(\text{OH})_3^-$ and $\text{Zn}(\text{OH})_4^{2-}$. The Zn speciation curves are similar at 0.1 M and 10 μM .

This section has described the hydrolysis reactions that all the first-row transition metal ions undergo. It is daunting how the differences among elements impact on the speciation chemistry summarized above. For example, the Zn speciation is very simple compared to the Cu speciation where Cu and Zn are adjacent first-row transition metal elements. Similarly, Ni and Cu are adjacent elements and the Ni speciation is much simpler than the Cu speciation. The most complex speciation was observed for Fe(III) and V. These two ions are very complex and the aqueous chemistry follows correspondingly to the speciation diagram for Fe(II) which is much simpler. These differences show that a change in oxidation state will dramatically change the solubility of the system. The stability of the complexes impact how the species exist in biological systems and, consequently, the applications to medicine.

4. Medicinal Uses of First-Row Transition Metals

Medicinal use of first-row transition metals in this document included both therapeutic and diagnostic uses of the first-row transition metals as well as examples of when the element is incorporated into materials that are used for medicinal purposes. In order for us to properly describe the uses of the each elements, we have included brief comments on basic information on the discovery

and the fundamental chemistry as well as the occurrence of the element and its essentiality for humans and potential essentiality in other organisms in the biosphere.

4.1. Scandium (Sc)

The first transition metal, named scandium (Sc, element 21), was isolated as an oxide by Lars Fredrik Nilson of Sweden in 1879, although the pure metal was not produced until the 1930s [3,13]. While Sc can exist in its metallic state, it is more commonly found in compounds and complexes as Sc(III), with predominantly octahedral geometry [16]. Scandium has a relatively high abundance in Earth's crust, comparable to cobalt (Co), but the presence of Sc-containing minerals is rare, with thortveitite being the main source [12,17]. Because of this scarcity, uses for Sc were not developed until recently [23,24] and there is still no known role for it in the biosphere.

Scandium is non-essential to human health and has been shown to be moderately toxic in a few toxicology studies [22–28]. It was found to be one of the more toxic rare-earth elements in mice [26]. It has also been tested in algae and *Caenorhabditis elegans*, a nematode used to model the nervous system; Sc was found to inhibit growth in algae and exhibit neurotoxicity in *C. elegans* [27,28]. Work carried out in the past decade suggests that the isotopes ^{44}Sc and ^{47}Sc are promising as imaging agents and therapeutics in nuclear medicine, but have yet to reach clinical trial in the USA and Europe as of July 2019 [8,29–34]. One promising technique is Immuno-Positron Emission Tomography, or Immuno-PET, which uses radiolabeled monoclonal antibodies to visualize tumor metastases and cancer [35,36]. Two clinical trials involving the treatment of various dental diseases have been completed using an Er,Cr:YSGG laser (erbium, chromium: yttrium, scandium, gallium, garnet) [37,38]. Another application of Sc for materials is in strengthening aluminum alloys [25,39] as well as a component in very strong lights [12]. Of the first-row transition metals, it is the least used element for medicinal purposes.

4.2. Titanium (Ti)

Element 22, titanium, was discovered in 1791 by William Gregor of Britain [3]. Titanium is widely distributed in Earth's crust, with its major mineral sources being ilmenite and rutile [13]. Aside from the metallic state, titanium can also exist as Ti(II) or Ti(IV), and in rare cases as Ti(III), with oxidation state IV being the most physiologically relevant form [10,40]. Titanium dioxide (TiO_2) is a common form of Ti and is widely used in sunscreen. The conventional amorphous form has a milky white appearance and is effective in scattering UV rays. However, the nanoparticle form of TiO_2 is transparent but still retains its scattering ability [41,42].

Titanium is found readily in the human body, although no reports suggest it plays an essential physiological role. It binds to human serum albumin and other proteins and is thus readily transported in the blood [43]. The element is not believed to be essential, although many reports in plants, animals, and human beings document its benefit. Titanium is able to support bone implant by osseointegration as was discovered in the 1950s [44,45]. The ability of Ti to integrate and be structurally accepted by bone without the requirement of soft tissue connection allows it to aid in healing and regrowth of bones [46].

Titanium is found readily in the human body, although no reports suggest that it plays an essential physiological role. It binds to human serum albumin and other proteins and is thus readily transported in the blood [43]. In medicine, Ti complexes and compounds have been examined as anticancer agents, in particular as titanocene dichloride. Even though the titanocene dichloride complex showed promising in vitro results and was evaluated in a clinical trial, it failed to perform satisfactorily in human studies. This is likely explained by the rapid hydrolysis of the complex [47]. However, studies continue to explore the potential of Ti as an anticancer agent and, recently, reports with dinuclear complexes are showing significantly improved anticancer activity against renal and prostate cancer cells [40,46]. Titanium dioxide (TiO_2) films have documented antimicrobial properties when irradiated by light, but there is a concern for the toxicity of TiO_2 nanoparticles [48].

The most common and well-known medical use of Ti is in implants [8,49]. Titanium and Ti-alloy implants are known to be biocompatible with excellent ability to integrate with bone. There are 488

clinical trials involving Ti are listed, of which 212 are completed. Therefore, there is no surprise that this element is used extensively, and many new applications are currently being investigated involving a wide range of applications ranging from dental implants to orthopedic prosthetics. The widespread applications of Ti have been driven by the belief that it is safe and inert to processing within the human body. This belief was based on simplistic studies in aqueous solution demonstrating the high stability of Ti-complexes or alloys at physiological pH values. Recently, however, reports have been made demonstrating that Ti can corrode, which can not only lead to implant breakage, but also formation of ROS species and production of a type IV allergen [50]. There are also reports of Ti(0) becoming physiochemically corroded to Ti(IV) ions which can result in inflammation and necrosis [49,51–53]. The leached forms of titanium, either soluble Ti(IV)tricitrate or as TiO₂ nanoparticles, have resulted in toxicity [40,52]. Considering the widespread use of TiO₂ in sunscreens and particularly in the form of nanoparticles, there are several UV and non-UV debilitating cellular effects caused by TiO₂ and it is important that the form and use of TiO₂ is carefully considered [41].

4.3. Vanadium (V)

Vanadium is element 23 and was first discovered by Andres Manuel del Rio in 1801 in Mexico. Unfortunately, four years later the discovery was withdrawn because del Rio had been convinced that the element was chromium (Cr) [3]. Thirty years later, V was rediscovered by the Swedish Nils Gabriel Sefström [3] who named it after the Nordic goddess of beauty and fertility, Vanadis (also called Freyja in Norse mythology). Vanadium exists in the Earth's crust in the form of numerous minerals as well as in fossil fuel deposits bound to porphyrin analogues [54–56]. It turns out that VO₂⁺-porphyrin analogs are among the most stable porphyrins [55] and, thus, are found in several coal deposits, such as Venezuelan coals. Processing of this coal results in a large release of vanadium-containing aerosols [54,57].

Figure 4 shows the mushroom *Amanita muscaria* that contains amavadin, which is a V(IV)-containing natural product of specific interest to the scientific community for not containing the V=O unit, common in V(IV) coordination complexes [58,59]. Although it has been controversial whether vanadium is an essential element for human beings [60], it is known to be essential for some organisms [61]. High levels of V are found in V-accumulating tunicates, and the form in these organisms have been explored and is currently believed to be the V-binding proteins (VanaBin) [61,62]. The function and role of vanadium in these organisms are still being investigated [61,62]. Other V-containing enzymes were isolated from certain types of algae, seaweed, and fungi, and the class of V-dependent haloperoxidases have been characterized extensively and the X-ray structures of the vanadium-dependent chloroperoxidase and the vanadium-dependent bromoperoxidase have been reported [61]. The vanadium nitrogenase from *Azobacter vinelandii* have recently been characterized spectroscopically [63–68].



Figure 4. A photo of the *Amanita muscaria* mushroom with the V(IV)-containing natural product amavadin. The image was reproduced from JJ Harrison/Wikimedia Commons under the Creative Commons Attribution-Share Alike 3.0 Unported license (<https://creativecommons.org/licenses/by-sa/3.0/deed.en>).

Vanadium in oxidation state V, in the form of vanadate, is a structural and electronic phosphate analog [63–66]. Vanadyl sulfate, a simple salt with V in oxidation state IV, is used as a nutritional additive by athletes to improve glucose metabolism [69]. As a phosphate analogue, it is a potent phosphatase and phosphorylases inhibitor [70,71]. Specifically, vanadate was first discovered to be a Na⁺- and K⁺-ATPase inhibitor [72] and later an inhibitor for ribonucleases [73], and, for some time, vanadate was added to buffers when isolating DNA because this protected the DNA strands from hydrolysis. Recently, the inhibition of protein tyrosine phosphatases have received interest, because this signal transduction enzyme has been implicated in the action of vanadium compound to reduced elevated blood glucose in diabetic mammals [70,71]. Both vanadate and vanadyl sulfate as well as one coordination complex, bis(ethylmaltolato)oxovanadium(IV), have been investigated for potential treatment against diabetes in Phase I and II clinical trials [69,74,75]. Vanadium coordination complexes also have activities as anticancer compounds [76,77], and recently both salts and select complexes were found to enhance an oncolytic virus, VSVΔ51, in combatting cancers that are resistant to existing therapeutics [78,79].

4.4. Chromium (Cr)

Chromium is element 24 and was discovered in 1798 by Nicholas Louis Vauquelin of France [3]. The physiologically relevant oxidation states are Cr(III), Cr(V), and Cr(VI). Cr(IV) can sometimes be observed in biological systems as an intermediate [20]. Chromium(III) generally has a coordination number of six with an octahedral geometry and, since it is hydrolytically stable at neutral pH, conversions involve redox processes [10,20]. Chromium(IV) tends to be an unstable intermediate under physiological conditions, preferring coordination number six with octahedral geometry [10,20]. Cr(V) and Cr(VI) are often found with lower coordination numbers. Chromic acid (HCrO₄) is a strong acid that is commonly used in acid baths for cleaning glassware. Much work has been done on the speciation of this element, and Cr(III) is reported to oxidize to higher and reduced forms [20]. Although Cr(III) is being taught as inert in introductory chemistry classes, this is only the case at neutral and slightly basic conditions.

The question of essentiality with Cr is complex because up until the 1980s, Cr was believed to be essential. Chromium(III) is therefore a component of various vitamin preparations and is still believed to be beneficial for the regulation of glucose metabolism. However, Cr is no longer believed to be essential by many scientists [80] and the matter of CrO₃- essentiality and its benefits is highly controversial despite a billion dollar industry supporting Cr additives [81]. The problem relating to the use of Cr(III) as a nutritional additive revolves around the fact that Cr(III) is not as stable as previously believed and will convert to the highly toxic Cr(VI) under biological conditions [49,82]. The major concern remains that some forms of Cr, generally the high oxidation states, are toxic as determined by various cancer tests, such as the Ames test [20,83–85].

Chromium has been reported to be beneficial for humans with impaired glucose metabolism and treatment was effective in normalizing glucose levels [86]. These studies were fueled by the report of a chromium-containing Glucose Tolerance Factor [87]. This material was reported to have beneficial effects on diabetics, and have carried through to clinical trials and other studies with Cr-containing materials [86]. Disagreements began to appear once the question of essentiality for Cr was questioned leading to the current general view, which no longer support the essentiality of Cr [80].

The risk of cancer with exposure to occupational hexavalent Cr (Cr(VI)) was studied more than 100 years ago [88]. Workers in certain industries such as chromate production, pigment production, and chrome plating have a significant greater increase in the risk for developing lung cancer [89]. Furthermore, Cr(VI) is classified as a known human carcinogen by the International Agency for Research on Cancer, known for causing cancer of the lung and positive associations with cancer of the nose and nasal sinuses [90]. However, conflicting evidence and analysis have been provided for stomach or other cancers, but a recent analysis reported that Cr(VI) does not pose a stomach cancer hazard in human beings [88]. Although Cr(III) may not have been reported to be toxic, when it oxidizes to Cr(VI), it is toxic [91]. Detailed speciation analyses have been carried out and demonstrate that Cr(III) is not as inert as previously believed, thus contributing to the debate on the safety of Cr-

containing food supplements readily available online and in food stores [49,82]. However, other studies have been carried out exploring the complexity of the issue because detoxification mechanisms are also in effect [85].

4.5. Manganese (Mn)

Element 25 is manganese, which was first isolated in its metallic form from pyrolusite in 1774 by Johann Gottlieb Gahn of Sweden [3]. For Mn, there are several oxidation states that are common under physiological conditions: II, III, IV, and VII. Six-coordinate octahedral Mn(II) is the most common of the physiologically relevant valencies and coordination geometries [10]. There is, however, some variability in coordination geometries for this metal in biological systems. For example, Mn(II) forms six-coordinate octahedral mononuclear complexes and dinuclear complexes but clusters with a Mn in coordination number of four or six.

Manganese is essential for humans and a multitude of other organisms, ranging from bacteria, to plants, to animals. The US Institute of Medicine updated the estimated average requirements and recommended dietary allowances for 22 elements for which there were sufficient data available. For adults, the tolerable upper intake level is set at 11 mg/day, while far less is recommended for children [92]. Manganese is less toxic than other transition metals such as Ni, and waterborne Mn is more readily taken up than dietary Mn [93]. However, Mn, as other essential elements, have a concentration range of acceptable range of oral intake illustrated in Figure 5.

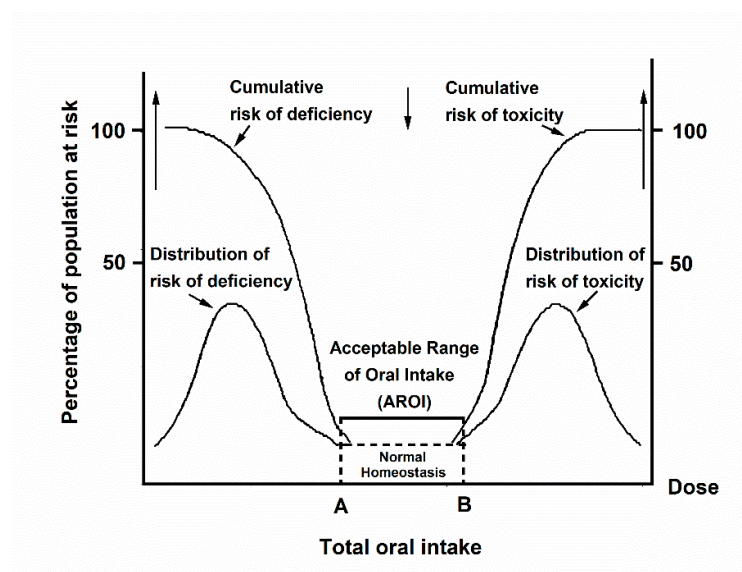


Figure 5. An illustration representing oral intake resulting in deficiency and overload of essential trace elements such as Fe, Cu, and Zn. The area between points A and B on the x-axis referred to as normal homeostasis, describes the ideal range of Cu for a normal and healthy organism. Reproduced with permission from Chambers et al. [94].

Manganese-based enzymes include hydrolases, superoxide dismutase, and photosystem II [1]. Several Mn-containing enzymes have the active site Mn ion involved in catalytic processes [82]. For example, glutamine synthase catalyzes the condensation of glutamate and ammonia to glutamine [95]. Glutamine synthase in mammals is mainly present in the brain astrocytes, liver, and kidneys. Brain astrocytes regulate glutamate and ammonium levels while recycling neurotransmitters [96]. Manganese complexes are now of interest as MRI contrast agents in part because of their presence in the brain (for references see Section 4.6).

Perhaps most well known is the role of Mn in photosystem II, which contains a Mn_4CaO_5 cluster [97]. Photosynthesis is a biochemical mechanism in plants by which chlorophyll absorbs light energy for photosynthesis. There are two families of reaction centers: type I reaction centers utilizing iron–

sulfur cluster proteins in chloroplasts and type II reaction centers utilizing a quinone terminal electron acceptor in plant chloroplasts. The oxygen-evolving complex is part of photosystem two and contains a Mn_4CaO_5 cluster [97].

Superoxide dismutase (SOD) enzymes are involved in scavenging radical oxygen species (ROS) including superoxide, and the mitochondrial forms of the enzyme contain Mn as a cofactor [98]. Other SOD enzymes contain Cu or Fe instead of Mn. Manganese can participate in Fenton reactions and, thus, induce oxidative damage as supported by toxicology studies in welders [99]. Small SOD mimics have received interest as new therapeutics as anticancer compounds [100]. Manganese-based SOD mimics are generally based on porphyrin, polyamine, and salen ligands and are thought to show anticancer effects due to the fact of their ability to act as pro-oxidants within cancer cells [100,101]. Manganese-containing catalase mimics target non-radicals such as H_2O_2 and reduces neurotoxicity, acting as pro-oxidants [102].

Manganese supplements are commonly sold to treat deficiencies which can lead to improper bone growth. However, Mn is known to have neurotoxic effects in high doses, sometimes leading to a Parkinson's-like disease called manganism [103,104]. This disease often presents itself after chronic exposure to Mn in excess of $5 \mu\text{g}/\text{m}^3$ and is distinguished from Parkinson's by a lack of Lewy bodies (protein aggregates in nerve cells) and no response to drugs used in the treatment of early Parkinson's [105]. Treatment has included chelation therapy, although the patient responses have not been encouraging, suggesting the damage had already occurred [106].

4.6. Iron (Fe)

Iron is element 26 and has been known for more than 1000 years since at least the Iron Age. While Fe is the most abundant metal on Earth, pure Fe is rare in the Earth's crust and generally comes from meteorites. However, Fe-containing minerals are readily available and often recognizable in nature with a warm rusty red color, although the common hematite and magnetite minerals appear as a darker red/black color [10]. Fe(II) and Fe(III) are the most physiologically common oxidation states although higher oxidation states are formed in some catalytic cycles. Iron complexes are commonly six-coordinate in an octahedral geometry, though a coordination number of five can be important in some systems.

Iron is an essential element in most, if not all, forms of life and a component in many biological processes with perhaps the most important being associated with respiration [6]. The complex relationships between the need to consume enough of an essential element and the problems associated with consuming too much is illustrated in Figure 5. However, Fe overload is a serious condition because the overload allows for sufficient Fe to engage in Fenton chemistry and ROS generation [107]. Formation of ROS is generally detrimental to an organism, so there are regulatory systems in place to maintain Fe homeostasis.

In blood, Fe is bound to a porphyrin, which is coordinated to the iron in the equatorial plane and, depending on the location of the complex, may contain one or two axial ligands [19]. This type of complex, known as a heme, is the major oxygen carrier in the blood. The Fe(II)-containing heme is not free but is bound to one of two proteins, hemoglobin in blood or myoglobin in muscle [6]. Hemoglobin exists in two forms: oxyhemoglobin when complexed to oxygen in arterial blood or deoxyhemoglobin when oxygen-free in venous blood [108]. The hemoglobin system is responsible for the red color of blood. For free hemoglobin is critical for life in cases when a ligand such as CO or CN binds to the heme, oxygen transport is no longer possible and the organism dies [109]. Treatment of such conditions include administration of 100% oxygen.

In addition to respiration, Fe is an important cofactor for many enzymes, too many to be described here and the reader is referred to reviews and textbooks on the topic of Fe metabolism [110]. Iron is generally a catalytically active metal ion that supports redox processes in enzymes such as oxidases, electron transfer reactions, and in plants it is involved in nitrogen fixation [6]. The plant enzyme nitrogenase contains a Fe-containing cluster. The protein transferrin is primarily responsible for transporting Fe in the blood throughout the body, including dietary Fe shown in a simplified schematic illustration in Figure 6 [111]. The Fe levels in the body are tightly regulated,

making Fe homeostasis an important medical field. Diseases from both Fe overload or deficiency are common. These problems are treated with Fe supplements or hemachromocytosis with various Fe chelators. Unfortunately, both Fe deficiency and overload conditions are common in our modern society.

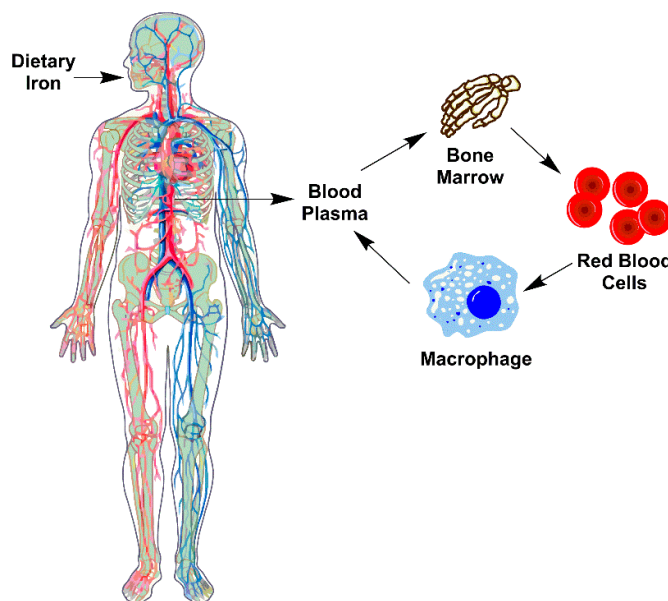


Figure 6. A simplified diagram of Fe metabolism from dietary Fe redrawn and modified from Sanghae and Nemeth [111].

There has been a significant amount of research done exploring the potential of Fe-based pharmaceuticals for treatment of cancer [112]. Because of the roles of Fe in biology, these applications are monitored carefully because doses that are too high will be detrimental [113]. Three classes of Fe compounds have been used [112], the largest group being that of ferrocene derivatives [114,115]. These organometallic compounds include ferrocenone, which is currently the only Fe-based compound used in the clinic [112]. One such ferrocene compound, ferroquine, is a derivatives which is currently in Phase II clinical trials [112,116]. In addition, a third group of ferrocene coordination compounds containing natural products have been reported with anticancer properties [115]. Coordination complexes are the second class of Fe-containing compounds have also recently been studied and they were found to have some beneficial effects. As described in detail elsewhere, these compounds are successful in treatment of several types of cancer including those that are resistant to cisplatin [112]. Although these complexes have not been investigated as extensively as ferrocene, recent studies suggest that there may be some potential applications of such systems. The third class of Fe-containing compounds recent investigation into Fe-chelators have yielded particularly interesting results [117]. A particularly intriguing system within this class of compounds, is when the chelator is a protein, such as lactoferrin. Lactoferrin is a non-heme protein binding Fe(III) at the same time as binding a carbonate anion [118]. Although it is in the blood, it does not appear to be involved in transport of Fe with the exception of lactoferrin from milk, which seems to be important for delivering Fe to newborns [107]. This system and its protolytic derivatives show anticancer properties particular when administered in combination with other agents. Recently other diseases are investigated as potential being treated with Fe-based compounds.

Recently, other applications and diseases have been investigated for treatment with Fe-based compounds. For example, Fe(II) and Fe(III) complexes are of interest as MRI contrast agents [119–121]. These complexes are alternative agents to the current standard agents that contain the lanthanide metal gadolinium, and provides options in cases when the MRI patient cannot clear the imaging agent, such as patients with kidney disorders [120]. Iron has well-characterized biochemistry

and predictable physiology, making it a promising candidate for new contrast agents [120]. However, such applications must take the patients' Fe levels into account due to the potential for Fe overload.

4.7. Cobalt (Co)

Cobalt, element 27, has been known for centuries for its ability to add a blue color to glass and ceramic glazes, but it was officially discovered by Georg Brandt of Sweden in 1735 [3]. Cobalt(II) complexes typically show a four-coordinate tetrahedral or six-coordinate geometry while Co(III) complexes are often six-coordinate octahedral coordination geometry [10]. Co-compounds are very colorful. For example, the color of CoCl_2 salt is based on hydration. The dry form of CoCl_2 is sky blue; however, as the compound absorbs water the color changes to purple and finally to pink. In Figure 7b, the color of purple CoCl_2 is compared to that of vitamin B_{12} (also referred to as cobalamin, see below) in the solid state and in solution.

Vitamin B_{12} is the most well-known bioactive Co-containing compound and is utilized by many organisms, from phytoplankton to humans, thus making Co an essential element to humans and many other organisms in the biosphere [122]. The vitamin's structure was solved in 1956 by the British scientist Dorothy Hodgkin and led to her receiving the 1964 Nobel Prize [123]. The structure of vitamin B_{12} is shown in Figure 7a illustrating the six-coordinate Co(III) in an octahedral geometry [10]. Vitamin B_{12} deficiency leads to fatigue, breathlessness, and poor memory [124]. Vitamin B_{12} deficiency is also found in older women that have lost the ability to extract B_{12} from foods. The condition of hypochlorhydria is found in about 47% of the population in the US caused by excessive use of antacids and low acidity in the stomach. These individuals are treated with injections of vitamin B_{12} when diagnosed.

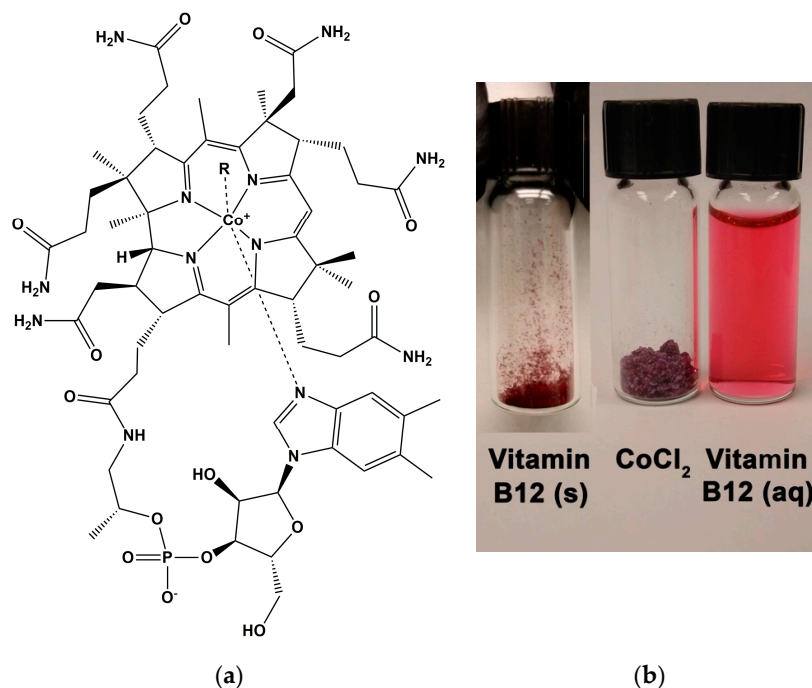


Figure 7. (a) The structure of vitamin B_{12} , where R is 5'-deoxyadenosyl, OH or CN; (b) solid vitamin B_{12} comes in the form of dark red crystals as opposed to cobalt(II) chloride, which forms blue crystals that turn purple with increasing amounts of absorbed water. When dissolved in water, vitamin B_{12} forms a pink solution.

Several forms of Co are currently used for medical purposes. Vitamin B_{12} is used in the treatment of acute cyanide poisoning in France [125] because Co(III), like Fe(III), also binds strongly to CN^- and, thus can extract the CN^- that is bound to the Fe(II) in the heme and regenerate the Fe(II)-heme complex so that it can carry oxygen. Early uses of cobalt chloride involved treatment of certain types

of anemia but it has since been replaced with synthetic erythropoietin [126]. Schiff base ligands form complexes readily with Co and have been used in a variety of medical applications. For example, the Co(III) Schiff base compound CTC-96 has completed Phase II clinical trial for the treatment of herpes simplex virus [127,128]. Compound CTC-96 is believed to prevent membrane fusion of the virus. Anticancer activity has been observed in a number of Co(II) and Co(III) Schiff base complexes [127,129]. Dinuclear heterometallic Co compounds have also been investigated, such as a cobalt-ruthenium cobaltocene derivatives which showed increased autophagic activity relative to the mononuclear Co derivative [130,131]. In addition, the radioisotope ^{60}Co has been used as a source of high-energy radiation to destroy cancerous tissue [132].

4.8. Nickel (Ni)

Element 28 is nickel, which was discovered in 1751 Axel Frederik Cronstedt of Sweden who later isolated it in 1754 [3]. The most common oxidation states for Ni are Ni(0) and Ni(II). Within these oxidation states, coordination numbers of four (square or tetrahedral geometry) and six (distorted octahedral geometry) are the most common [10]. Heteronuclear metal compounds have been suggested to be precursors to metalloenzymes and early representative of Ni-Fe-containing enzymes because they are able to catalyze a range of reactions [133]. Nickel has a high affinity for porphyrins and since it is the most stable porphyrin derivative, it is often found in coals. Exploitations of coal as an energy source releases Ni-containing aerosols [54,57].

The essentiality of Ni is somewhat controversial, with scientists supporting both positions. While no essential role for Ni has been identified, it is a cofactor in multiple enzymes in bacteria, archaea, and fungi [134]. One well-known Ni-containing enzyme is urease, which catalyzes the hydrolysis of urea [135]. Since urease, as a Ni-dependent enzyme, is often found in human gut bacteria, human gut health is correlated with the presence of Ni and indirectly important to human health [136]. Conversely, urease is virulence a factor for *Helicobacter pylori*, which is a causative agent of stomach ulcers [137]. Thus, the presence of Ni in vitamins supports the well being of beneficial bacteria by inhibiting some of the 40 known pathogenic species potentially residing in the human gut and, thus indirectly benefitting the human host [135].

Nickel is a common component of strong alloys, some of which have been used in implantable medical devices such as joint replacements or arterial stents. For example, The Ti-Ni alloy nitinol is used for arterial stents because of its excellent shape memory [138]. Nickel compounds have also been used to support weak bones in osteoporosis as well as to increase Fe absorption in anemia. However, there is a duality to Ni, since Ni sensitization is linked to many cases of allergic contact dermatitis, such as in body jewelry [136,139]. There have been recent cases of individuals developing Ni irritation and allergies to these implants [49]. Furthermore, the US Environmental Protection Agency has determined that Ni dust and Ni sulfide are human carcinogens. A few pharmaceutical applications of Ni are emerging. For example, Ni is one of the metals of choice in the formation of metal-containing complexes that bind to nucleic acid quadruplexes that are currently being investigated for potential use as anticancer agent [140].

4.9. Copper (Cu)

Copper is element 29 and has been known for over five thousand years. It is one of the few transition metals known to exist in nature in its native metallic form. While it can exist as Cu(I), Cu(II), and Cu(III), the most common oxidation state under physiological conditions is Cu(II). For Cu(II), the most common coordination numbers are four and six, with four generally having square planar geometry and six having distorted octahedral geometry, whereas Cu(I) prefers tetrahedral geometry [10]. The different geometric coordinations properties of Cu(I) and Cu(II) have been utilized to create molecular motion in rotaxanes [141]. This work was awarded the Nobel Prize in 2017.

Copper is an essential element to many, if not all, organisms and is found as a cofactor in a multitude of enzymes, typically coordinated to histidine, cysteine, and methionine ligands [10,113]. Copper(II) is known to coordinate both to structural or functional sites for proteins [142]. The most well-known Cu-containing enzyme is cytochrome c oxidase, a large transmembrane protein that is

vital to cellular respiration by translocating protons across the membrane to create an electrochemical gradient that drives ATP synthesis [143]. Two heme groups and two Cu sites, Cu_A and Cu_B, are present within cytochrome c oxidase. The second Cu ion Cu_B forms a binuclear center with the Fe in a heme and together they are responsible for the reduction of molecular oxygen to water. At the same time, Cu_A is involved in electron transfer to an internal heme [9,144,145]. In Cu_B, the Cu ion is coordinated to three histidine residues via the imidazole rings and has a trigonal pyramidal geometry [9]. The multivalent Cu_A site is two copper ions, both with tetrahedral geometry, bridged by two cysteine residues [10,145].

Much like Fe, Cu deficiency and overload lead to diseases. Figure 5 illustrates the potential Cu levels that an individual would experience under various doses. In excess, Cu causes toxicity via ROS generation which leads to DNA damage and is commonly treated by administration of Zn(II), which induces synthesis of small proteins rich in cysteine known as metallothioneins [113,146,147]. These proteins have a high affinity for both dietary and gastrointestinal Cu, binding Cu and sequestering it. Truncated metallothioneins were found to have Cu bound to cysteines with trigonal geometry [10]. Copper is known to cause oxidative stress in the brain, linking it to neurodegenerative diseases such as Alzheimer's and Parkinson's [148]. Copper(II) shows two different pH-dependent binding modes in the native amyloid- β peptide, both of which bind in a distorted square-planar geometry [149]. A deficiency of dietary Cu leads to anemia-like symptoms as well as neurological issues such as myelopathy [150,151].

Copper complexes, like Fe complexes, are of interest for anticancer therapeutics. Several Cu complexes have been investigated for treatment against cancer [152,153]. These complexes are classified as chelators and ionophores, where chelators remove Cu to limit angiogenesis and cancer progression while ionophores transport Cu into cells where the ions can then exert cytotoxicity [153]. Copper anticancer compounds have been reported with a variety of ligands, such as thiosemicarbazones, thiosemicarbazides, dithiocarbamates, pyridine N-oxides, phenanthrolines, and naphthoquinones, though a multitude of others have also been studied [154,155]. Investigations of dinuclear metal complexes involving Cu have also been prepared and reported to have anticancer properties. Tetrathiomolybdate is the most well-studied of the Cu-chelating compounds and has advanced to several Phase II and III clinical trials for treatment of various cancers as well as Wilson's disease, a genetic disorder that causes an accumulation of Cu in the body and is currently treated with tetrathiomolybdate [156].

Over 280 applications of Cu-containing compounds and materials have been investigated for treatment in human beings. Of these clinical trials, 184 studies have been completed and 98 are currently recruiting or active. Some of these applications include intrauterine devices (IUD). Although non-metal devices have been used for hormonal IUDs, Cu remains the most used non-hormonal devices with 150+ million being used worldwide [157]. The generally accepted mechanism for contraceptive IUDs is inflammation of the uterine lining, allowing for increased presence of white blood cells that prevent the fertilization of oocytes [158]. Other applications include Cu-infused textiles for the prevention of hospital-acquired infections. These textiles take advantage of Cu's antibacterial properties, making a type of self-sanitizing bandage to cover the wound [159,160].

4.10. Zinc (Zn)

Zinc is element 30 on the periodic table. The pure metallic form was discovered in 1746 by the German Andreas Sigismund Marggraf [3]. Zinc exists in two oxidation states: the metallic form, Zn(0), and as the cation Zn(II). Because Zn(II) has a ligand stabilization energy of zero in all potential geometries, no coordination geometry is more stable than others. Zinc is often found in four-coordinate tetrahedral geometry or six-coordinate octahedral geometry [10]. Surveys of the Cambridge Structural Database show zinc ions in four- and six-coordinate systems with frequencies of 59% and 23%, respectively [161].

Approximately one hundred years after its initial discovery, Zn(II) was reported to be essential to life and its importance in biology has been thoroughly investigated since then. As an essential element, deficiency can result in a variety of health disorders including hearing and vision

impairment [10]. Since Zn is a non-redox active metal ion, its use complements that of Fe and Cu, which are also widespread in biology. The lack of redox activity may be one reason that the abundance of Zn rivals that of Ca and is important as a cofactor for metabolic enzymes, transcription factors, and facilitators of gene expression. For example, Zn is required in more than 200 transcription factors. Zinc present in vitamins and nutritional supplements. It is also in zinc lozenges which are recommended for treatment of the common cold and reduce the duration of the illness [162]. It has been proposed that the Zn may work by preventing the rhinovirus from propagating and supporting its infestation of the host, though this is a topic of debate [162].

Zinc is a key component in a number of enzymes as well as DNA-stabilizing proteins and other structural components in biology. The coordination geometry of Zn varies with its role, be it structural or catalytic [163]. When Zn(II)'s role is to structurally organize proteins, its coordination numbers are 79%, 6%, and 12%, respectively, for four, five, and six coordination [161]. Even though five-coordinate geometry is usually rare, it is found in Zn porphyrins [161]. One important group of proteins is the Zn finger proteins, which are critical for the organization and transcription of DNA [164]. Figure 8 shows DNA transcription assisted by a Zn finger protein.



Figure 8. A Zn finger protein domain assisting in DNA transcription, where DNA is colored orange, the protein is gray, and green spheres are Zn. The image was generated with VMD software from PDB file 1A1L [165,166].

Although a non-redox active metal ion, it is now known that Zn(II) acts as a second messenger that can activate some signaling pathways within a few minutes of an extracellular stimulus such as the release of Zn(II) from intracellular compartments. Since Zn(II) cannot passively diffuse through cell membranes, homeostasis requires Zn transporter proteins that are controlled by different mechanisms. There are two families of Zn(II) transporters: SLC30A (ZnT transporters) and SLC39A (ZIP transporters) [167]. These proteins all have transmembrane domains with both N- and C-terminal peptides in the cytoplasm (ZnT transporters) or both C- and N-terminal peptides in the extracellular space (ZIP transporters). The ZnT transporters are Zn exporters, transporting Zn from the inside of the cell to the outside, while ZIP transporters are importers, transporting Zn into the cell from outside. Most of the ZIP transporters reside on the plasma membrane and transport Zn(II) into the cell, but ZIP7 resides in the endoplasmic reticulum membrane and ZIP13 is in the Golgi membrane. Both ZIP7 and ZIP13 transport Zn(II) from these stores to the cell. Recent discoveries investigating the Zn(II) ZIP transporters have linked these proteins to Zn(II) signaling related to cancer. Figure 9 is a schematic showing the members of the LIV-1 family of ZIP transporters and the different cancers in which they have been implicated. Most of these studies involve biochemical

investigations and specific details on how that particular transporter works. Details regarding each of these ZIP transporter proteins have been reviewed elsewhere [168].

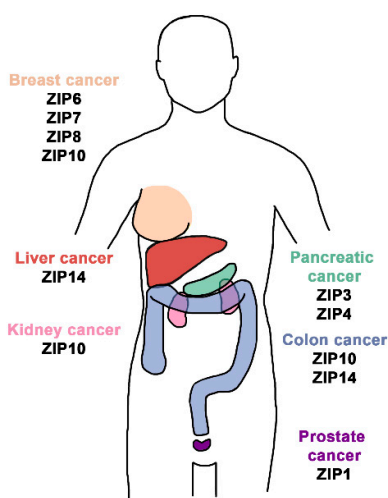


Figure 9. A Schematic showing the association of the members of the LIV-1 Zn-ZIP transporter family and the different cancers that have been implicated these transporters. Redrawn from an image in Reference [168].

Zinc has been used in several medications including antibacterial ointments. There is also evidence of Zn as an active ingredient in some ancient medicines [169]. The form of Zn(II) in antibacterials is ZnO, possibly in nanoparticle form [170]. Furthermore, Zn and Ni are the metals of choice in the formation of metal-containing complexes that bind to nucleic acid quadruplexes that are currently being investigated for potential use as anticancer agents [154]. The use of Zn(II)-containing coordination compounds has been reported in animal studies against diabetes [171] which may stem from the fact that it binds with high affinity to regulatory protein tyrosine phosphatases, one of the classes of proteins that uses Zn(II) as a signaling molecule [168,172].

5. Discussion

As described above, all first-row transition elements have applications in medicine whether it is well understood or currently under development. Their involvement ranges from limited applications of non-essential elements such as Sc, for which there is relatively little information available compared to the essential elements such as Fe, Cu, and Zn which have numerous applications.

For some of the elements, the potential for essentiality is debated in the literature, but these issues are complex because trace elements such as V are often administered as an impurity with other supplements such as Fe-supplements. Furthermore, as in the case of Ni, its presence in the human gut serves a protective function by eliminating pathogenic species that otherwise might invade the human gut. However, strictly defined, non-essential elements are elements that do not have a defined role in humans such as Ti, V, Cr, and Ni are known and are surprisingly found to have many applications, particularly when compared to, for example, the essential elements Mn and Co.

It is, however, interesting to note that most essential transition elements are first-row transition elements. Furthermore, the late first-row transition metals, with the exception of Ni, are essential to humans. This is interesting and presumably a combination of the properties that the elements have as well as the properties of the molecules that make up the biosphere. If proteins were made up from different components, presumably the essential elements would consist of different elements.

6. Conclusions

In this manuscript, we present the entire periodic table of medicines but focus our in detail description on the properties and applications of the first-row transition metal ions in medicine. This compilation of knowledge will inform the reader regarding the applications of the different elements and metal ions in medicine as well as provide a brief but somewhat basic description of each element. In addition, this review highlights the fact that metal ions, as counter ions, bind strongly to proteins or other biological systems and often do so in order to exert their beneficial effects. There are too many potential problems if, for example, a metal ion such as Fe(II) or Fe(III) is not bound efficiently because free ions will engage in Fenton chemistry which will result in the formation of ROS and thus result in toxicity.

The importance of metals in life sciences includes a role as positively charged counterions that coordinate to negatively charged biological residues. Essential metal ions will have a structural or a catalytic function and, thus, bind to proteins, RNA, DNA or other biological structures in order to exert a particular role. This is an overarching role of the first-row transition elements although multiple specific detailed actions for each element exist while exerting this role.

Applications of metal compounds as medicines or diagnostic agents are very different than the corresponding use of organic compounds. This is because the bioprocessing of an organic drug will break down into metabolites, whereas a metal compound will lead to the simple metal ion after bioprocessing. Since the only way to remove a metal ion from a cell is to excrete it, a more likely fate of the metal ion after processing that it will bind to some metabolites that can bind or chelate ions. Such metabolites, in addition to proteins, are naturally occurring ligands in cells such as citrate, phosphates, amino acids, and carbohydrates that will form complexes with any free metal ion when they are located in close proximity to each other. The lifetime of a metal-based drug is therefore extended beyond that of its initial form, and its chemistry should be considered as well as its uptake and excretion of it and compounds formed by chemical and biological processing. The study of metal ions in medicine and any biological system that is charged should include consideration of the speciation. Although speciation chemistry is sometimes ignored, it is of importance for explaining some properties observed with different metal ions. In this review, we included a brief summary of the speciation of the first-row transition metal ions and as such, linked the fundamental aqueous chemistry to the medicinal applications of these metal ions in an attempt to link the chemical properties to that of their respective roles in biological systems and medicine.

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