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Environmental and Biomedical Applications of Natural Metal Stable Isotope Variations

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Iron in human blood is enriched in lighter iron isotopes relative to diet and the geosphere.

IMAGE: 3D ILLUSTRATION OF BLOOD CELLS. © YAKOBCHUK / DREAMSTIME.COM

Metal stable isotopes are now being used to trace metal contaminants in the environment and as indicators of human systemic function where metals play a role. Stable isotope abundance variations provide information about metal sources and the processes affecting metals in complex natural systems, complementing information gained from surrogate tracers, such as metal abundance ratios or biochemical markers of metal metabolism. The science is still in its infancy, but the results of initial studies confirm that metal stable isotopes can provide a powerful tool for forensic and biomedical investigations.

KEYWORDS: metal contaminant tracing, metal homeostasis, multi-isotope approach, isotope effects

INTRODUCTION

Metals occur in the environment as natural constituents of rocks, waters, and organisms, and they play an important role in a wide range of inorganic and biologic processes. Metals can also contaminate the environment, often reaching concentrations that are toxic to organisms.

Metal isotopes have proven incredibly powerful for determining sources of metals and for understanding processes that affect metals in a variety of Earth science disciplines, although the vast majority of isotopic studies conducted over the past several decades have focused on understanding Earth's history and evolution. For example, strontium, neodymium, and lead radiogenic isotopes have been used to understand rock petrogenesis from hand specimen to global scales, while calcium and iron stable isotopes have been increasingly used to understand paleochemistry of the oceans (e.g. alkalinity, redox). Metal isotopes are now rapidly finding their role in the environmental and biomedical sciences, where they can be used to "fingerprint" metal contaminants to help identify sources, or to study metal transfer processes in complex systems such as the human body. In both of these fields, diagnosis and treatment are the main goals. Thus, in environmental studies, diagnosis might determine the source of a metal contaminant, while treatment might assign responsibility and initiate or monitor remediation. In biomedical applications, diagnosis might determine the presence of a systemic disorder, while treatment might involve drug therapy or changes in diet or lifestyle habits. Here we focus on the

use of metal stable isotopes as a diagnostic tool in environmental and biomedical applications, a frontier aspect of the rapidly evolving field of metal stable isotope science.

USING ISOTOPES TO POINT THE FINGER

Metal contaminants are widespread in the environment, and they pose a significant threat to humans and ecosystems. Metals may be transported for long distances along atmospheric,

hydrologic, and food vectors, and thus can be difficult to trace back to their sources. Metal contaminant tracing has traditionally relied on using the abundance ratios of metals or radiogenic isotope surrogates. However, many environmentally important metals have multiple stable isotopes that can now be precisely quantified. As a result, research teams worldwide have begun exploring whether variations in isotope composition can be used to fingerprint sources of metal contaminants and decipher processes affecting the distribution of metals in the environment. Chromium (Cr), copper (Cu), zinc (Zn), and cadmium (Cd) form a particularly interesting group for demonstrating processes that can lead to variations in isotope composition, because Cr and Cu have multiple oxidation states in nature, whereas Zn and Cd do not. Here we explore some recent advances in our understanding of isotope fractionation processes of these metals.

Chromium

Chromium has numerous industrial applications, including use in electroplating, in leather tanning, as pigment in paint, and as an anticorrosion agent. It is stable at the Earth's surface in two oxidation states: hexavalent Cr, Cr(VI), which occurs mainly as the toxic, water-soluble oxyanion chromate ($\text{Cr}_2\text{O}_4^{2-}$); and trivalent Cr, Cr(III), which is nontoxic, insoluble in water, and the common form in minerals, such as chromite (FeCr_2O_4). The measured range of $^{53}\text{Cr}/^{52}\text{Cr}$ in natural materials is ~5‰, reflecting the range measured for naturally occurring Cr(VI) in groundwater (Izbicki et al. 2008). Both inorganic and microbially mediated reduction of Cr(VI) to Cr(III) have been shown to induce isotope fractionation, with the product Cr(III) formed at any step of the process being 3 to 4‰ lighter than coexisting remnant Cr(VI) (Ellis et al. 2002; Sikora et al. 2008). The fact that the oxidized species, Cr(VI), is heavier than the reduced species, Cr(III), is consistent with observations for other redox-sensitive elements, such as selenium (Johnson et al. 2000) and mercury (Bergquist and Blum 2009 this issue).

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Given the contrast in isotope composition between coexisting Cr(III) and Cr(VI), Cr stable isotopes should be useful for recognizing reduction of toxic Cr(VI) to nontoxic Cr(III) in contaminated groundwater and ideally for distinguishing between natural and anthropogenic Cr(VI). The results of a pilot study (CH2MHill 2007) carried out at the Pacific Gas & Electric Compressor Facility in Hinkley, California (made famous in the movie *Erin Brockovich*), provide an example of this application. From 1952 to 1966 at this site, cooling tower water containing Cr(VI) leaked into the underlying aquifer, creating a plume of Cr(VI)-contaminated groundwater that by 2000 had migrated more than 3 km from the source. For the pilot study, 20 groundwater samples were analyzed for Cr stable isotope composition (Bullen 2007). The data form a well-organized trend in Cr(VI)– $\delta^{53/52}\text{Cr}$ space, with near-facility (contaminant) and regional groundwater samples defining the extremes and samples from the contaminant plume plotting in between (FIG. 1). In this case, the isotope ratios effectively distinguish the natural and anthropogenic Cr(VI) end members. The composition of samples from the

(Cu_2S), and enargite (Cu_3AsS_4); and divalent Cu, Cu(II), which is the common form in aqueous solution. In natural materials, the measured range of $^{65}\text{Cu}/^{63}\text{Cu}$ is approximately 9‰ for solid samples and 3‰ for water samples (Larson et al. 2003; Borrok et al. 2008). Mathur et al. (2005) demonstrated that abiotic oxidative dissolution of sulfide minerals results in the product aqueous Cu(II) being ~1.4‰ heavier in terms of the $^{65}\text{Cu}/^{63}\text{Cu}$ ratio than Cu in chalcocite and ~3.0‰ heavier than Cu in chalcocite. However, when the microbe *Acidithiobacillus ferrooxidans* was added to the experimental medium, the observed fractionation between aqueous Cu and mineral Cu decreased to sub-per mil levels in both cases, presumably from preferential association of aqueous ^{65}Cu with the bacterial cell walls. Based on these experimental results and field studies at sites impacted by acid mine drainage, Borrok et al. (2008) and Kimball et al. (2009) proposed that $^{65}\text{Cu}/^{63}\text{Cu}$ ratios of streamwater in Cu-mineralized areas could be useful for ore prospecting, contaminant-remediation efforts, and determining the site-specific role of microbes.

Zinc

Zinc is used in electroplating, metal alloys, pigment in paint, agricultural fertilizers and pesticides, roofing material, and television-screen phosphors. Zn is also a major global pollutant. In natural materials, the measured range of $^{66}\text{Zn}/^{64}\text{Zn}$ is approximately 2‰. Unlike Cr and Cu, Zn is stable at the Earth's surface only in divalent form, Zn(II), and thus observed stable isotope variation cannot be attributed to multiple redox states. On the other hand, Zn has a relatively low boiling point (~910°C) compared with that of Cr or Cu, within the range of operating temperatures for ore smelting. Thus Zn can evaporate from ore during smelting, which would favor escape of light Zn isotopes in the exhaust, as demonstrated by Mattielli et al. (2009), and retention of heavy Zn isotopes in the slag residue, as shown by Sivry et al. (2009). Kavner et al. (2008) established that electroplated Zn, reduced to metallic state from a large pool of divalent Zn, is isotopically light compared to the parent solution, potentially resulting in a large pool of isotopically light electroplated Zn in the environment. In addition, Weiss et al. (2007) demonstrated that Zn adsorption by organic complexation is selective for the heavy Zn isotopes, resulting for example in ombrotrophic peat samples that have heavier Zn isotope compositions than any potential source. On the other hand, Borrok et al. (2008) pointed out that Zn uptake by microorganisms is selective for the light Zn isotopes. Thus there are several isotope fractionation processes for Zn that might modify its isotope composition in the environment.

Cadmium

Cadmium is used primarily in Ni-Cd batteries, metal alloys, electroplating, pigment in paint, and electronic components. It is commonly associated with Zn and thus has also become an environmental contaminant. In natural materials, the measured range of $^{114}\text{Cd}/^{110}\text{Cd}$ is approximately 0.5‰. Like Zn, Cd is stable at the Earth's surface only as divalent Cd, Cd(II), and thus observed stable isotope variation cannot be attributed to multiple redox states. However, Cd has an even lower boiling point (~760°C) than Zn, and like Zn, Cd in ores likely evaporates during smelting, favoring escape of light Cd isotopes in the exhaust, as Cloquet et al. (2006) recently demonstrated. Cd behaves like Zn during electroplating (Kavner et al. 2008), resulting in a large pool of isotopically light Cd in the environment.

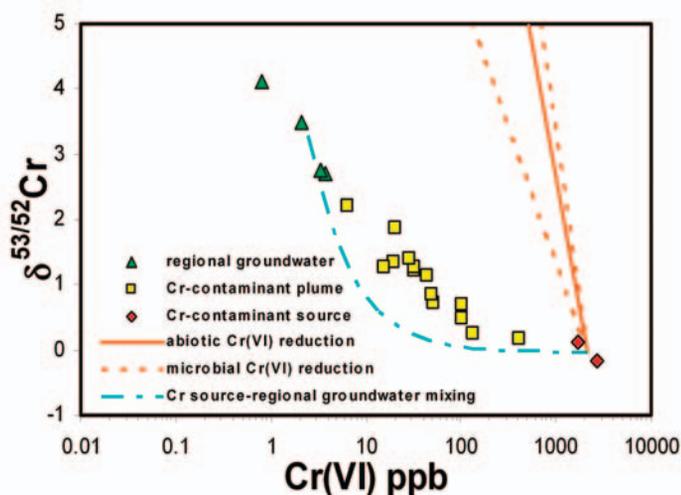


FIGURE 1 $\delta^{53/52}\text{Cr}$ and Cr(VI) concentration data for groundwater at the Hinkley, California, site. $\delta^{53/52}\text{Cr}$ is standard δ notation in terms of $^{53}\text{Cr}/^{52}\text{Cr}$; zero on the δ scale is NIST 979 Cr. Cr-contaminant source samples were collected at the PG&E compressor facility; Cr-contaminant plume samples were collected down gradient from the compressor facility within the defined Cr(VI) plume. Regional groundwater samples were collected just up gradient, just down gradient, and well away from the plume. The Cr source–regional groundwater mixing curve is calculated for mixing between the Cr-contaminant source and average regional groundwater. The abiotic Cr(VI) reduction vector is from Ellis et al. (2002); the microbial Cr(VI) reduction vectors are from Sikora et al. (2008) and show the range of fractionation observed in their experiments. The composition of Cr(VI) remaining in solution following partial reduction is expected to evolve along these vectors; their slopes remain constant on the diagram regardless of starting point.

contaminant plume, which lie intermediate to model curves for reduction of the Cr(VI) contaminant and dilution by advective mixing with regional groundwater, probably resulted from a combination of these two processes.

Copper

Like Cr, Cu has a wide range of industrial applications, including use in electrical wires, metal alloys, boat paint, water and gas supply pipes, and coins. Also like Cr, Cu is stable at the Earth's surface in two oxidation states: monovalent Cu, Cu(I), which is the common form in sulfide minerals such as chalcopyrite (CuFeS_2), chalcocite

Isotopic Multitracing: An Example Using Cd and Zn Stable Isotopes

Tracing metal pollutants in the atmosphere using stable isotopes is a rapidly expanding field. To date, Cd and Zn have received the most attention, but studies that include both of these metals are rare. Regardless, a recent review of Zn isotope systematics by Cloquet et al. (2008) included an intriguing graph of Zn and Cd stable isotope data for contaminated soil samples collected close to a Pb-Zn refinery in northern France (Fig. 2). The aim was to identify sources of Cd and Zn in the soil samples. Three end members in Cd-Zn isotope space were proposed: refinery slag, refinery chimney dust, and distant background agricultural topsoil. The data suggest an important role for chimney dust and a lesser role for slag in the soils, a conclusion that makes sense given sample proximity to the refinery. Such information could be useful for contaminated-soil remediation. This multitracer approach is likely to be broadly applicable, and the remarkable uniformity of $^{66}\text{Zn}/^{64}\text{Zn}$ in ZnS ores (Sonke et al. 2008) should aid intersite comparisons of smelter-pollution impact.

Other possible metal sources to consider are petroleum products and vehicle emissions, waste incineration products, particulate rubber from tires, fly ash and residues from coal burning, wood-burning emissions, and degraded electroplated metal dusts. These additional sources have yet to be systematically characterized for metal stable isotope composition, pointing to exceptional research opportunities. Regardless, a fascinating multitracer approach is emerging, one that will be strengthened by incorporating other metal stable isotope systems, such as Cr, Cu, and Hg, in the site assessment.

BIOMEDICAL APPLICATIONS: ISOTOPIC PROBES OF SYSTEMIC FUNCTION IN HUMANS

Studies of disorders related to absorption, utilization, or loss of metals by the body currently rely mainly on biochemical markers in serum, plasma, and urine that are either directly or indirectly associated with metal metabolism. Variations in isotope composition induced by physiological processes have the potential to become a novel, complementary class of clinical markers for assessing impairments in metal metabolism. Using knowledge of isotope fractionation of metals such as Ca and Fe in the geosphere and biosphere, a few research groups have explored this phenomenon in humans. Theoretically, the magnitude of metal isotope fractionation depends on transfer efficiency between organs, tissue, and chemical species within the body as well as on uptake efficiency and systemic losses. The metabolism of any higher organism can be described in terms of such element transfer processes, which form the basis of homeostasis (i.e. the tendency to maintain a stable condition) for any essential metal. The desire to gain insight into metal metabolism using isotopes has spurred unanticipated collaborations between the metal stable isotope and medical science communities, two of which are described here.

Calcium Isotope Signals in Urine: Towards an Indicator of Bone Loss

Bone, the largest repository of Ca in humans, is constantly being resorbed and reformed (i.e. "remodeled") and thus figures prominently in Ca homeostasis. Skulan and DePaolo (1999) reported that for vertebrates, the $^{44}\text{Ca}/^{40}\text{Ca}$ ratio of bone is $\sim 1.3\%$ less than that of Ca circulating in plasma from which bone forms due to preferential incorporation of light Ca in newly formed bone. The empirical model of Ca isotope behavior in vertebrates proposed by these researchers suggests that when the rates of bone resorption

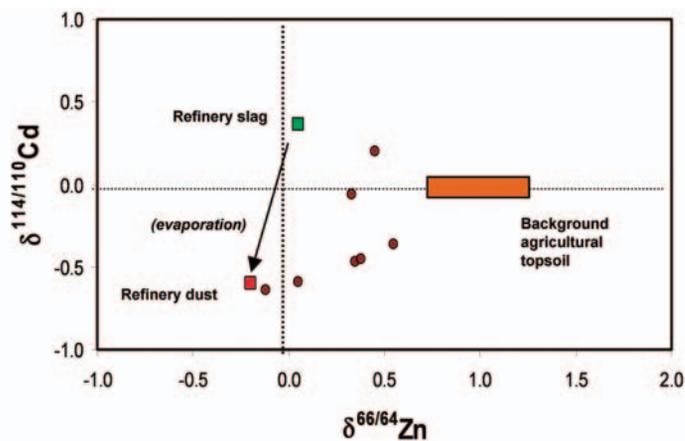


FIGURE 2 Cd-Zn isotope systematics for soil samples from northern France and possible Cd and Zn sources, both measured and interpreted. $\delta^{114/110}\text{Cd}$ is standard δ notation in terms of $^{114}\text{Cd}/^{110}\text{Cd}$; zero on the δ scale is Johnson Mathey Cd. $\delta^{66/64}\text{Zn}$ is standard δ notation in terms of $^{66}\text{Zn}/^{64}\text{Zn}$; zero on the δ scale is Johnson Mathey Zn. Data for contaminated soils (circles) and refinery dust and slag are from Cloquet et al. (2008). The field for background agricultural topsoil was interpreted by Cloquet et al. (2008): the range of $\delta^{66/64}\text{Zn}$ is based on measured data for Zn in ombrotrophic peat samples (Weiss et al. 2007) collected well away from Zn-contamination point sources; $\delta^{114/110}\text{Cd} = 0\text{‰}$ is derived from the observed small variability of Cd isotope composition in natural materials. The vector labeled "evaporation" shows how light dust composition results from boiling of Cd and Zn in a smelter.

and formation are equal and $^{44}\text{Ca}/^{40}\text{Ca}$ of diet is constant, the difference in $^{44}\text{Ca}/^{40}\text{Ca}$ between bone and soft tissue or plasma is constant (i.e. at steady state). The model also suggests that when the rate of bone resorption exceeds that of formation (i.e. bone loss), $^{44}\text{Ca}/^{40}\text{Ca}$ of soft tissue/plasma should decrease relative to the steady-state value, and vice versa. Thus, over time, $^{44}\text{Ca}/^{40}\text{Ca}$ of soft tissue/plasma proxies such as urine may provide a noninvasive measure of bone mineral balance.

The results of a NASA-sponsored study of the effectiveness of countermeasures to bone loss during spaceflight provide a glimpse into the potential use of this approach. For the study (Skulan et al. 2007), Ca isotope ratios were measured in urine samples from 10 subjects who underwent 17 weeks of bed rest in an attempt to induce bone loss in a controlled clinical setting. Of the study participants, a control group had bed rest only, a second group received alendronate (a drug for osteoporosis therapy that reduces bone resorption), and a third group performed occasional resistive exercise; all participants received the same diet over the study period. Pooled urine samples were collected for Ca isotope analysis before, at 2 or 3 points during, and after 17 weeks of bed rest. The difference in average $\delta^{44/40}\text{Ca}$ values of urine samples for the three study groups from the average $\delta^{44/40}\text{Ca}$ values of urine for each group at the start of bed rest are plotted against time in Figure 3. Comparison to initial $\delta^{44/40}\text{Ca}$ values of urine was necessary to offset the $>2\%$ difference in initial steady-state $\delta^{44/40}\text{Ca}$ values among individuals, presumably resulting from differences in factors such as diet and Ca metabolism. Thus all group $\delta^{44/40}\text{Ca}$ averages are zero initially.

After the start of bed rest, negative $\delta^{44/40}\text{Ca}$ values are consistent with net bone resorption while positive values are consistent with net bone formation according to the proposed isotope fractionation model. In this context, the group receiving alendronate and the group participating in resistive exercise had on average positive values, while the control group had on average negative values. There

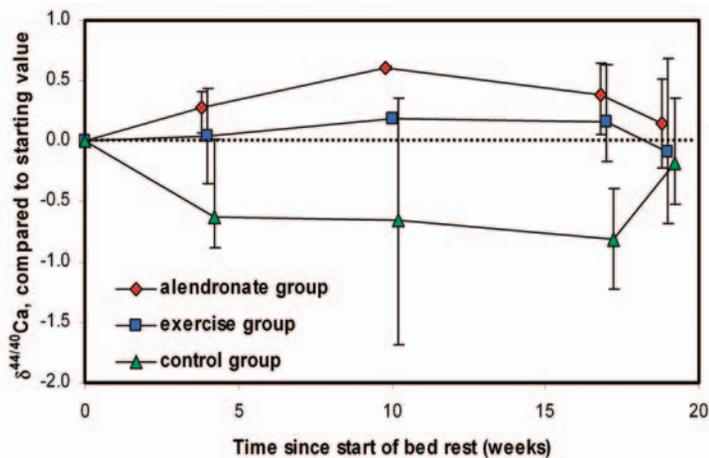


FIGURE 3 Group-averaged $\delta^{44/40}\text{Ca}$ of urine samples for three different study groups collected during a bed-rest experiment. $\delta^{44/40}\text{Ca}$ is standard δ notation in terms of $^{44}\text{Ca}/^{40}\text{Ca}$ ratio. Values are calculated as the difference from the average $\delta^{44/40}\text{Ca}$ value for each group at the start of the experiment. Positive values are consistent with net bone formation, negative values with net bone resorption. Vertical bars on each data point show the range of composition observed for each group at the given time. Data were collected at $t = 0, 4, 10, 17,$ and 19 weeks; the results for the alendronate and control groups are offset slightly from these times in order to allow the range bars to be discernable. MODIFIED FROM SKULAN ET AL. 2007

was considerable intragroup variability for relative $\delta^{44/40}\text{Ca}$ at any time, as shown by the range bars in FIGURE 3, indicating inter-individual variations in response to treatment. Regardless, changes in bone mineral balance suggested by the isotope signals were consistent with measurements of bone mineral density of the femoral neck and lumbar spine of study participants (Skulan et al. 2007). Processes other than bone formation, such as Ca absorption in the kidney and intestine, may lead to differences in isotope composition between Ca in bone, soft tissue or plasma, and urine. For example, in this study all urine samples had $^{44}\text{Ca}/^{40}\text{Ca}$ ratios greater than that of dietary Ca, possibly reflecting an isotope effect during renal absorption of Ca similar to that recently proposed by Heuser and Eisenhauer (2009). More studies are needed to improve understanding of Ca isotope fractionation in the human body and thus put urine signals into proper context.

Iron Isotope Signatures in Blood

Iron is handled differently by the human body than all other physiologically essential elements. It is the only element that the body cannot excrete in case of excessive absorption. Although Fe is the fourth most abundant element in the Earth's crust, most life forms have struggled over evolutionary time spans to satisfy their Fe needs. For humans, Fe is soluble at gastric pH but insoluble at the neutral pH of the intestine, the primary site of mammalian Fe absorption (Miret et al. 2003). As a result, the human body has evolved into a virtually closed system for Fe. Levels of functional Fe for oxygen transport, oxygen storage, and cellular function are maintained by intestinal regulation of Fe absorption in concert with Fe deposition in or release from storage organs (Bleackley et al. 2009). Pathological conditions develop if regulation of Fe absorption is persistently impaired. These conditions include Fe deficiency and anemia at one extreme and Fe accumulation and overload at the other. Fe deficiency is associated with

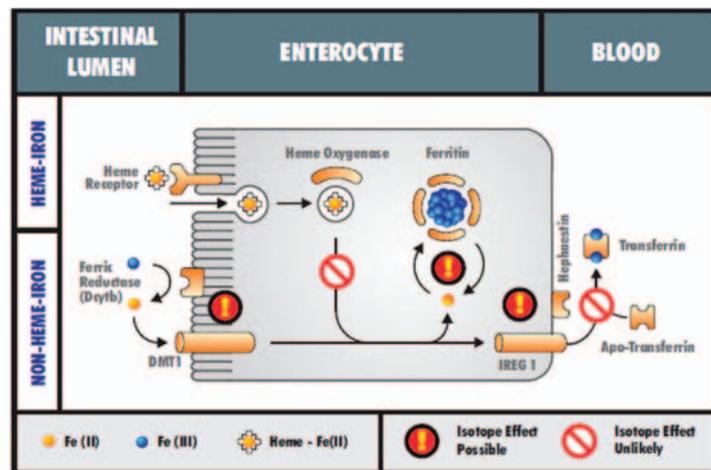


FIGURE 4 Transfer of heme Fe (from foods of animal origin) and nonheme Fe (from plant foods) through the intestinal mucosa into blood. Nonheme Fe is taken up by divalent metal transporter 1 (DMT1) after reduction to Fe(II). Heme Fe enters the epithelial cell by endocytosis, and Fe is released by the action of heme oxygenase. Nonheme Fe as well as Fe released from heme are either transported by Fe regulatory protein-1 (IREG-1) from the epithelial cell to the blood or deposited in ferritin. Isotope fractionation may occur by preferential uptake of lighter Fe isotopes by the DMT-1 pathway and release through IREG-1 and/or during deposition of heavier Fe isotopes in ferritin. In contrast, endocytosis of heme isotopomers (small relative mass differences) and release of Fe from the heme molecule (a quantitative process) are not expected to be isotope selective.

decreased work performance, lower resistance to infection, and growth deficits, while Fe overload may lead to tissue damage as a result of oxidative stress (Edison et al. 2008).

Tools to reveal impairments of Fe absorption regulatory systems are needed to help identify individuals or population groups at risk of becoming Fe deficient or overloaded. However, impairments of Fe absorption itself or its regulatory mechanisms are nearly impossible to assess in an individual using conventional techniques for measuring Fe absorption, because efficiency of absorption from diet can vary from less than 1% to nearly 100% within a single day. Recently it has been suggested that Fe isotope signatures in blood can fill this niche as an integrating, long-term measure of Fe absorption. Iron in human blood was found to be significantly enriched in light Fe isotopes relative to Fe in the Earth's crust, with young adult males having lighter Fe than women of fertile age (Walczyk and von Blanckenburg 2002). As opposed to other clinical measures of Fe status, the Fe isotope composition of blood is virtually not affected by diurnal and day-to-day variations in the individual because of low Fe turnover (Ohno et al. 2004). Per day, less than 0.05% of body Fe is lost and replaced through diet in a healthy adult.

Differences in Fe isotope composition of blood of individuals do not directly reflect differences in diet, because blood Fe is lighter than Fe of either animal or plant origin (Walczyk and von Blanckenburg 2002; Guelke and von Blanckenburg 2007). Likewise, mass-sensitive loss of Fe isotopes in digestive juices is not a primary determinant of the Fe isotope composition of blood in humans. Preferential absorption of light Fe isotopes in the intestine appears to be the most probable mechanism (a schematic of possible fractionation pathways is shown in FIGURE 4). This would also explain differences in young adult males and females that were not observed in older subjects (Krayenbuehl et al. 2005). On average, Fe losses are higher

by 30% in females than in males because of menstrual blood loss. To balance extra Fe needs, Fe absorption in young women needs to be more efficient than in men and postmenopausal women. This is consistent with observed differences in the Fe isotope composition of blood from the studied population groups.

As a secondary mechanism, inhomogeneous distribution of Fe isotopes among body tissues following absorption must be considered. For example, Fe in the liver, the major Fe storage compartment in the body, was found to be isotopically heavy relative to blood and muscle tissue, which had similar Fe isotope composition in any individual (Walczyk and von Blanckenburg 2005). Release of heavy Fe from the liver would explain relatively heavy Fe in hemochromatotic patients who have undergone blood-letting therapy to remove accumulated iron from the liver (Krayenbuehl et al. 2005; Stenberg et al. 2005). As with Ca, more studies are needed to improve understanding of Fe isotope fractionation in the human body, so that blood signals can be put into proper context.

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THE FUTURE

We have only begun to scratch the surface of the possibilities for using metal stable isotopes in the environmental and biomedical sciences. Indeed, each of the isotope systems discussed here could be applied equally well to either environmental or biomedical problems, and all that is required to realize this potential is imagination and access to a mass spectrometer. New applications will flourish over the next several years for an array of metal stable isotope systems, and advances are likely to result from creative interdisciplinary collaborations that build on the strengths and unique scientific cultures of the individual researchers.

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