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A State-of-the-Science Review on Metal Biomarkers

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Abstract

Purpose of Review—Biomarkers are commonly used in epidemiological studies to assess metals and metalloid exposure and estimate internal dose, as they integrate multiple sources and routes of exposure. Researchers are increasingly using multimetal panels and innovative statistical methods to understand how exposure to real-world metal mixtures affects human health. Metals have both common and unique sources and routes of exposure, as well as biotransformation and elimination pathways. The development of multi-element analytical technology allows researchers to examine a broad spectrum of metals in their studies; however, their interpretation is complex as they can reflect different windows of exposure and several biomarkers have critical limitations. This review elaborates on more than 500 scientific publications to discuss major sources of exposure, biotransformation and elimination, and biomarkers of exposure and internal dose for 12 metals/metalloids, including 8 non-essential elements (arsenic, barium, cadmium, lead, mercury, nickel, tin, uranium) and 4 essential elements (manganese, molybdenum, selenium, and zinc) commonly used in multi-element analyses.

Recent Findings—We conclude that not all metal biomarkers are adequate measures of exposure and that understanding the metabolic biotransformation and elimination of metals is key to metal biomarker interpretation. For example, whole blood is a good biomarker of exposure to arsenic, cadmium, lead, mercury, and tin, but it is not a good indicator for barium, nickel, and uranium. For some essential metals, the interpretation of whole blood biomarkers is unclear. Urine is the most commonly used biomarker of exposure across metals but it should not be used to assess lead exposure. Essential metals such as zinc and manganese are tightly regulated by homeostatic processes; thus, elevated levels in urine may reflect body loss and metabolic processes rather than excess exposure. Total urinary arsenic may reflect exposure to both organic and inorganic arsenic, thus, arsenic speciation and adjustment for arsebonetaine are needed in populations with dietary seafood consumption. Hair and nails primarily reflect exposure to organic mercury,

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Declarations

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except in populations exposed to high levels of inorganic mercury such as in occupational and environmental settings. When selecting biomarkers, it is also critical to consider the exposure window of interest. Most populations are chronically exposed to metals in the low-to-moderate range, yet many biomarkers reflect recent exposures. Toenails are emerging biomarkers in this regard. They are reliable biomarkers of long-term exposure for arsenic, mercury, manganese, and selenium. However, more research is needed to understand the role of nails as a biomarker of exposure to other metals. Similarly, teeth are increasingly used to assess lifelong exposures to several essential and non-essential metals such as lead, including during the prenatal window.

Summary—As metals epidemiology moves towards embracing a multi-metal/mixtures approach and expanding metal panels to include less commonly studied metals, it is important for researchers to have a strong knowledge base about the metal biomarkers included in their research. This review aims to aid metals researchers in their analysis planning, facilitate sound analytical decision-making, as well as appropriate understanding and interpretation of results.

Keywords

Metals; Review; Biomarkers; Arsenic; Barium; Cadmium; Lead; Mercury; Nickel; Tin; Uranium; Manganese; Molybdenum; Selenium; Zinc

Introduction

Epidemiological studies traditionally examine exposure-outcome relationships one at a time. With the advancement of novel analytical and statistical methods and the development of programs such as the Human Health Exposure Analysis Resource (HHEAR) to support the measure of multiple exposures [1], the field of environmental epidemiology is quickly moving to study environmental exposures in ways that more closely resemble real-life exposure mixtures [2–4].

Exposure to metals and metalloids (referred to throughout as “metals” for simplicity) is widespread, and four of the top ten chemicals of major public health concern recognized by the World Health Organization are metals (arsenic, cadmium, lead, and mercury) [5]. Chronic exposure to certain metals contributes to the development of adverse health outcomes across the life course, including but not limited to cardiovascular disease [6], kidney disease [7–9], some cancers [10, 11], adverse birth outcomes [12–14], neurocognitive outcomes [15], and bone disease endpoints [16].

Biomarkers are commonly used in epidemiological studies to assess metals exposure and estimate internal dose, as they integrate multiple exposure sources, including air, water, and food. Multi-element techniques such as inductively coupled plasma mass spectrometry (ICP-MS) can quantify metal levels with high sensitivity and specificity. In addition, relatively new tools such as Bayesian Kernel Machine Regression [17] and Weighted Quantile Sum Regression [18] enable the statistical analysis of large panels of metals. The interpretation of those analyses, however, can be complex. Metals have both shared and unique sources and routes of exposure (Fig. 1); some metals share common absorption, transformation, or elimination pathways, while others differ in their metabolic route; and not all biomarkers are effective measures of metals exposure. As metals epidemiology embraces a multi-metal/

mixtures approach and metal panels expand to include less commonly researched elements, such as nickel, tin, and molybdenum, it is important for researchers to have a strong knowledge base about the metals studied.

In this review, we discuss sources of exposure, biotransformation and elimination, and biomarkers of exposure for 12 metals, including 8 non-essential elements (arsenic (As), barium (Ba), cadmium (Cd), lead (Pb), mercury (Hg), nickel (Ni), tin (Sb), uranium (U)) and 4 essential elements (manganese (Mn), molybdenum (Mo), selenium (Se), and zinc (Zn)), commonly used in multi-metal epidemiologic analyses. This review aims to aid metals researchers in their analysis planning, analytical and statistical approaches, and interpretation of results.

Methods

Search Strategy and Data Abstraction

To identify the most informative literature for the metals included in the review, we searched across PubMed, Google-Scholar, and EMBASE using free text, key words, and MeSH terms. A separate search was conducted for each section (i.e., sources of exposure, biotransformation, and biomarkers), and refined for every metal, consistently including MeSH terms such as “biomarkers”[MeSH Terms], “biotransformationmation” [MeSH Terms], “absorption” [MeSH Terms], and “metabolism” [MeSH Terms]. No language or time window restriction was applied. We excluded non-original research, case reports, case series, and non-peer-reviewed literature except from institutional reports (i.e., Center for Disease Control and World Health Organization reports). We included a comprehensive selection of systematic reviews, meta-analyses, randomized controlled trials, and observational studies. If available, we primarily relied on longer follow-up, larger sample size, and more recent human studies. In vitro and animal studies were included to elaborate on emerging biomarkers. After the inclusion and exclusion criteria, a total of 521 unique records were identified, including laboratory, animal, and epidemiological studies.

Results

Non-essential Metals

Table 1 includes a summary of the most commonly used biomarkers, the exposure period reflected, and other considerations for the non-essential metals included in this review. Metals are presented alphabetically. Figure 1 displays their major sources of exposure.

Arsenic

Arsenic is a metalloid found in inorganic (arsenite and arsenate) and organic (arsenobetaine, arsenosugars, monomethyl, and dimethyl As) forms. Their toxicity, metabolism, sources of exposure, and effects on human health greatly differ [19, 20]. Because inorganic arsenicals and their methylated metabolites are considerably more toxic than the organics (especially seafood arsenicals), we address them separately.

Major Sources of Exposure—Inorganic As can be released into water from the natural erosion of rocks and soil [19, 21] and can be taken up by plants' root systems [22]. Inorganic As contamination of soil and water is also a result of anthropogenic activities, such as mining; coal-burning power plants; smelting operations [23]; wood preservatives; agriculture, where it was used as a pesticide prior to 1960 [24]; urban runoff, and various industrial waste sources [19]. These activities can lead to the mobilization of As from soil, landfills, or residue deposits into ground and surface water [19, 25–30]. Inorganic As can also be found in air as a mixture of arsenite and arsenate suspended as particulate matter [31], although non-occupational exposure via air is thought to be minimal in most populations, except for areas with As-contaminated coal burning [19]. The major route of exposure to inorganic As is through the ingestion of contaminated drinking water and food. More than 100 million people worldwide rely on water contaminated with inorganic As above 10 μg/L [32] (the WHO, US Environmental Protection Agency, and European Union standard), including 2 million people in the US [20], above 10 μg/L (the WHO, US Environmental Protection Agency, and European Union standard). When water As exposure is low, food is the major source of exposure [33, 34]. The primary contributors to dietary inorganic As intake are vegetables, fruits and fruit juices, and rice [35, 36]. Organic As is found in fish and shellfish, predominantly in the forms of arsenobetaine, arsenosugars, and arsenolipids [37]. It is also a component of some herbicides and anti-microbial additives such as roxarsone and nitarsone, which were used to increase efficiency in animal poultry feed [38]. The approval of As-based drugs in poultry production was withdrawn by the FDA in 2016 in the USA, after it was found that these arsenicals could transform into inorganic As [39]. Additionally, organic As is the active principle of antiparasitic drugs such as melarsoprol, which is used as a treatment for trypanosomiasis (sleeping sickness) and leishmaniasis [40]. Melarsoprol and inorganic arsenic are also used in the treatment of certain types of leukemia, myeloma, and other neoplasia [41, 42]. Organic As in air is rare, except in areas with intensive use of arsenical pesticides [43].

Absorption, Biotransformation, and Elimination—Inorganic arsenic is absorbed in the gastrointestinal (GI) tract, transformed through a series of methylation and reduction processes, and excreted primarily through the urine [19]. Throughout the metabolic process, species with different toxicities and elimination rates are formed. Trivalent and pentavalent inorganic arsenicals undergo two sequential methylation reactions to form monomethyl (MMA) and dimethyl (DMA) As. Inorganic and monomethylated forms of As have higher cytotoxic activity [44]. Methylation occurs mostly in the liver and requires the enzyme As methyl transferase (AS3MT), with S-adenosyl methionine as the methyl donor. Once formed, DMA and to a lesser extent MMA are rapidly excreted in urine. Methylation plays a crucial role in increased As elimination and decreased tissue retention [20, 45]. Organic As species such as arsenobetaine and arsenocholine are not metabolized, do not enter cells, and are excreted mostly unchanged in the urine [46]. Arsenosugars on the other hand have a complex metabolism and can be transformed into up to 12 As metabolites, including DMA, oxo-DMA, and rare species such as oxo-DMAA, thio-DMAA, thio-DMAE, and thio-arsenosugar [47, 48]. Their toxicity is believed to be limited [49]. Urinary excretion is the main route of elimination for both inorganic and organic As species. Inorganic As is

excreted in three phases: the majority is eliminated within the 4 first days after exposure, and 2 longer-term components eliminated at 1 week and up to 38 days [50].

Genetic variants in AS3MT have been associated with different As elimination rates and variable profiles of inorganic and methylated As species in urine, suggesting a genetic determination of As metabolism capacity [19]. Arsenic methylation is strongly influenced by the availability of methyl groups and co-factors involved in the one-carbon metabolism pathway, which are provided by nutrients, including vitamins B2, B6, B9 (folate) B12, choline, and betaine [51]. Nutritional deficiencies of B vitamins have been associated with increased toxicity of inorganic As in humans [52]. Supplementation with folic acid, other methyl donors, and compounds that interact with one-carbon metabolism have been associated with an increased metabolism and excretion rate of inorganic As in randomized clinical trials [53, 54]. Sex differences in As metabolism are well known. Women have a greater As methylation capacity compared with men, likely due to their higher phosphatidylethanolamine N-methyltransferase activity, which is involved in one-carbon metabolism and regulated by estrogen [55, 56]. For the same reason, As metabolism rapidly increases during pregnancy [57, 58]. Children have been reported to have a more efficient methylation activity than their parents [59, 60], potentially because of a more efficient second methylation step in children compared with adults [61].

Biomarkers—Total As in urine is one of the most commonly used biomarkers of As exposure in epidemiologic studies [62]. Several studies have reported strong correlations between urinary As and As in drinking water and rice intake [63–65]. Given the elimination phases of As, urinary As primarily accounts for exposures that occurred within the previous month [66, 67].

Importantly, total urine As reflects exposure to both organic and inorganic As. Thus, in populations with fish and seafood intake, total urinary As may primarily reflect organic arsenicals, in which case this biomarker will not reflect toxic inorganic As species well [68]. Therefore, when fish and seafood intake is prevalent, As speciation and adjustment for arsebonetaine is needed to distinguish between inorganic and organic arsenicals [69–71]. In the absence of seafood intake, the general proportions of As metabolites in urine have been reported to range from 10 to 30% for inorganic As, from 10 to 20% for MMA, and from 60 to 70% for DMA [44]. Similar to urinary As, blood As also reflects both organic and inorganic As. However, As speciation in blood is more complex than that in urine because concentrations are generally much lower [19]. In the absence of seafood consumption, the proportions of As metabolites in blood are different from those found in urine. Previous studies have reported the following proportions for blood: 43% for DMA, 30% for MMA, 13% for As III, and 13% for As V [72]. Inorganic arsenic travels through the blood and has a high affinity for keratin-rich tissues [50]. Hair, clipping from all ten toenails, and/or fingernails are used as biomarkers of past exposure. Fingernails generally represent exposures that occurred in the previous 6 months, while toenails, which have a slower growth rate, represent exposures from the previous 6 to 12 months [20]. For hair, every 1 cm from the scalp represents exposure from a prior month [73]. Environmental decontamination is needed to obtain reliable measurements from these tissues [19]. Moderate to high correlations have been reported between toenail, fingernail,

hair, and urine As concentrations, particularly in populations with high levels of inorganic As exposure [74]. Increasing evidence suggests that a toenail sample at a single point in time could represent a good biomarker for long-term exposure, when external exposures are consistent. However, validated protocols are needed to reduce measurement error from analytical methods in As toenail determination [19, 74]. Inter-individual differences in toenail growth rates may also contribute to differences in the time window of exposure that is reflected by the biomarker. Although few studies have investigated placental As as a biomarker of exposure, a study of private well users in the USA reported positive and significant correlations between As concentrations in the placenta and As concentrations in maternal urine, maternal and infant toenails, and drinking water [75].

Barium

Barium is rarely found in its inorganic form. It is usually combined with other elements, forming species such as barite (BaSO4), Ba chloride (BaCl2), or carbonates (e.g., Ca (Ba) CO3). These species have different solubilities, which has implications for their bioavailability [76, 78].

Major Sources of Exposure—Barium is an alkaline metal that occurs naturally in the earth crust, rocks, and coal [76, 78, 79]. It can be released into water from natural erosion. Traces of Ba from natural sources are ubiquitously present in food and water. Recent anthropogenic activity has intensified the burden of exposure to this metal [80]. Several activities, particularly petroleum and steel industries, drilling activity, and shale gas exploration [78], have increased the amount of Ba in soil, water, and air. Barium compounds are also used in the production of plastics, electronic devices, bricks, paper, glass, and cosmetics [77, 81, 82], pigments, aluminum, and sugar refining and fertilizers [76, 83]. In the last 40 years, Ba has also been widely used as a contrast medium in esophageal and GI tract function testing, and as a treatment for lower GI tract bleeding, among other medical applications [84, 85]. The main route of Ba exposure in the general population is through ingestion of contaminated food and water [76, 78], followed by inhalation from ambient air [76, 78]. Plants that grow in soil with high Ba concentrations can accumulate this metal, contributing to dietary intake [86]. Major dietary sources of Ba exposure include legumes and nuts, such as pecans, peanuts, and brazil nuts, which may contain Ba concentrations as high as 4,000 μg/g [76, 77, 87–90]. Other foods such as cabbage, soybeans, dairy products, and some processed foods have high Ba concentrations [77, 88, 91, 92]. Ba levels in water are variable. Ba in groundwater is frequently associated with radium, adding its toxicity to radium radionuclides such as 226Ra and 228Ra, with half-lives of more than 1000 years and 6 years respectively [78]. Ba is commonly found in urban air pollution particulates (mostly as $BaCl_2$ and $BaSO_4$) due to fuel exhaust and waste burning[76].

Absorption, Biotransformation, and Elimination—The absorption of Ba in the GI and respiratory tracts depends on the solubility of its chemical form. For example, highly soluble species such as $BaCl_2$ and $BaCO_3$ are more likely to be absorbed than others (e.g., $BaSO_4$). The absorption of Ba compounds into the bloodstream is highly variable and ranges from 1 to 60% of total intake [76], with higher absorption rates observed after longer durations of exposure [93] and among fasting individuals. In contrast, Ba absorption

decreases if there is a high concentration of competitive ions in the GI tract, such as calcium, phosphorus, and zinc [78]. Substances such as sodium alginate [94] have also been shown to reduce Ba absorption in the GI tract; in contrast, lysine and lactose [95] facilitate its absorption. Ba prevents calcium absorbance in pancreatic islets, which can lead to an increased release of insulin [96]. Ba does not undergo metabolic transformation in the body [62]. Once absorbed, it is rapidly cleared from the bloodstream, with 90% distributed to bone, followed by teeth, heart, lung, skin, adipose, connective, and other tissues [76, 97]. Barium has relatively short half-life and is eliminated from the body within 3 to 42 days; the half-life of barium in bone tissue is 50 days. Ninety percent of Ba administered intravenously for medical procedures as well as for other routes of absorption is excreted into feces and urine within this period [76, 97], with ~ 75% eliminated within 3 days. In the kidney, Ba is reabsorbed in the renal tubules, which decreases its urine excretion rate [77]. The rate of fecal Ba elimination is at least 2–3 times higher than the elimination through urine, and it is mediated by mechanisms such as pancreatic secretions, saliva, or direct excretion through the intestine wall; biliary excretion is only responsible for a small fraction of its fecal elimination [98]. Ba can act as an antagonist of potassium, and vice versa, by blocking the potassium channels of sodium–potassium pumps located in cell membranes [99], which reduces the concentration of extracellular potassium leading to hypokalemia [92]. Potassium can be used as an antidote for acute Ba intoxication [100–102].

Biomarkers—Barium can be detected in blood, urine, feces, and other biological tissues such as the placenta, teeth, and bone [77, 103–107]. Fecal and urinary Ba concentrations reflect recent exposure, within the previous 3 days and up to 2 weeks [97]. Overall, there is a need for studies which investigate correlations between environmental Ba concentrations and levels in urine and other biomarkers [76, 78, 108].

Cadmium

Major Sources of Exposure—Cadmium can naturally occur combined with other metals such as Zn, Pb, and copper in Cd-containing ores [109]. Human activities, including mining, smelting, industrial production of batteries, plastic and solar cells [110], fossil fuel and waste burning, and phosphate fertilizers, are the main sources of environmental Cd and the primary sources of soil and water Cd-contamination [90, 111]. Plants, including tobacco, can bioaccumulate Cd when they are grown in contaminated soils, incorporating this toxicant into the food chain and tobacco products [112, 113]. Tobacco smoke is a major source of Cd exposure. It is estimated that exposure to Cd in smokers is at least 10 times higher than in nonsmokers, adjusting for dietary intake [111]. Cd exposure can also occur as a result of secondhand smoke [114]. Decreases in population mean blood Cd levels have been reported in epidemiologic studies following reductions in smoking prevalence [20, 115]. The main source of Cd exposure among non-cigarette smokers is diet. Green-leaf vegetables such as spinach and lettuce and grains and seeds such as peanuts, soybeans, and sunflower seeds contain particularly high concentrations of Cd [111]. Consumption of shellfish and offal/ organ meat also contributes to Cd exposure [116, 117]. Cadmium can also be found in air as a component of particulate matter air pollution, especially in areas with high levels of ambient air pollution, such as urban areas and areas with heavy industrialization [118].

Absorption, Biotransformation, and Elimination—Cadmium absorption rates through the GI tract and inhalation are variable and range from 1 to 25% [111, 119, 120]. Absorption rates are influenced by several factors, including particle size for inhalation exposures, the solubility of certain Cd salts in biological fluids (e.g., Cd chloride is highly soluble), and the availability of cellular transporters. In drinking water, Cd is typically found in its ionic form, while in food it is usually linked to proteins (e.g., metallothionein) and other molecules [111]. Cadmium can use several transporters, including zinc and iron transporters, calcium channels, glutathione transporters, and divalent metal transporters (DMT1), which facilitate Cd absorption [111]. An inverse correlation between body iron and Cd absorption has been identified by previous studies [121]. While the molecular mechanisms are unclear, a dysregulation of DMT1, a metal transporter protein in the GI tract may partially explain this phenomenon. On average, the accumulation of Cd is higher in women compared with men at equal exposure levels, possibly due to differences in DMT1 expression and to the lower iron stores in women compared to men [20, 121, 122]. Zinc supplementation can reduce Cd absorption in the GI tract and induce the synthesis of metallothionein and a favorable redox homeostasis, suggesting a potential antagonist effect on Cd [123]. A recent study identified a 28% heritability for urinary Cd concentrations. Genetic variants linked to an increased expression of glutathione transporter ABCC1 may have a role in individual susceptibility to Cd absorption and internal dose [124]. Cadmium does not undergo metabolic transformation. Once it enters the bloodstream it primarily binds to metallothionein, forming metallothionein-Cd complexes. These complexes are distributed through the body, accumulating in the liver, bones, and kidneys [125].

In the kidney, [90, 111, 126] metallothionein is filtered by the glomeruli and reabsorbed in the proximal renal tubule, where free ionic Cd is released into the kidney cortex. Ionic Cd can cause renal toxicity by inducing oxidative stress, inactivation of metal-dependent enzymes, and activation of calmodulin and other enzymes, among other mechanisms [111, 127]. When free Cd concentrations in the renal cortex exceed 50 μg/g, Cd cannot be captured by metallothionein, causing nephrotoxicity. Less than 0.01% of the Cd body burden is eliminated by urinary excretion every day, which leads to a chronic accumulation of Cd in the kidney. This accumulation usually peaks after 50 to 60 years of exposure and then stabilizes due to the onset of Cd-induced renal injury, as well as the physiological loss in the renal cortex due to aging, which results in higher excretion of Cd in urine [128]. The half-life of Cd in the kidney is estimated to range between 6 and 38 years [129]. In contrast with chronic exposure, short-term exposure to Cd does not typically cause visible impacts on renal function. Cadmium also accumulates in the liver, where its half-life is estimated to range from 4 to 19 years [111].

Biomarkers—Cadmium can be measured in blood, urine, feces, placenta, and preferentially in soft tissues, including the liver and kidneys. Blood Cd is commonly used to assess recent exposure. Cd accumulates in erythrocytes and its half-life is around 100 days [20]. However, there is a slow component in blood, for which the half-life is 7–16 years; this component can also be indicative of internal body burden [90, 111]. Urine Cd is a biomarker of total body burden and long-term cumulative exposure due to its accumulation in the renal cortex for years and its slow rate of elimination in urine [130, 131]. However,

in populations where kidney function is compromised (e.g., renal injury from Cd-induced damage, age, other comorbidities) urinary Cd should be interpreted with caution. In these populations, the rate of Cd excretion increases, and urinary Cd no longer reflects body burden [111, 132]. Previous studies have documented a high correlation between total Cd exposure and urinary Cd concentrations [133–135] and low intra-individual variability, even in populations exposed to low levels [132, 136, 137]. Therefore, a single spot urine measurement can likely be used as a reliable biomarker of chronic exposure. Emerging biomarkers to detect early stages of Cd-induced nephrotoxicity include urinary measures of Kim-1 and beta2-microglobulin. However, their use is still generally limited to in vitro and animal studies [127]. Fecal Cd is reported to be a good biomarker of dietary Cd intake and indicates recent exposure, reflecting a combination of absorbed Cd, which is eliminated at a similar rate in urine and feces, and unabsorbed Cd from the diet [111]. Hair, fingernail and toenail Cd concentrations are not good biomarkers of exposure and are poorly correlated with smoking. The use of nails as biomarkers of exposure has been implemented in pilot studies identifying a low correlation between nail and blood Cd [138]. Cadmium levels in organs including the liver and kidneys can also be directly assessed using non-invasive techniques such as X-ray fluorescence analysis or neutron activation analysis. However, these measurements are limited by low sensitivity and are usually reserved for monitoring highly exposed workers rather than the general population [111]. Maternal smoking and Cd concentrations in both maternal blood and urine have each been associated with placental Cd concentrations across multiple studies [139–147]. In contrast, correlations between placental and cord blood Cd have been less consistent, likely because the placenta serves as a partial barrier to this metal; placental Cd concentrations have been reported to be higher than in maternal blood [139, 143, 148].

Lead

Major Sources of Exposure—The general population is exposed to Pb from air, drinking water, food, and indoor dust [149]. Lead does not undergo degradation over time in the environment. As a result, most individuals, particularly those living in urban areas, are exposed to high levels of Pb from previous decades' emissions. Before the 1990s, the main sources of Pb exposure were the combustion of leaded gasoline and Pb-based paint. Although Pb fuel additives were banned in 1995 in the USA [150], some are still in use for farm equipment, aircraft, and marine engines [149, 151, 152]. Other sources of exposure include waste, coal and oil burning, renovation of historical Pb-based paints or Pb-based paints in older housing, tobacco products, secondhand smoke, cosmetics, and electronic products [20]. The increasing amount of e-waste (discarded electronic devices) is also an emerging source of metal exposure, from dumpsites and informal recycling activities for Pb, Hg, and other toxicants [153]. Lead contamination in drinking water is mainly due to the corrosion of Pb-based pipes [154, 155]. Lead has also been documented in certain foods and herbs, including spices imported into the USA, as a result of athmospheric deposition, bioaccumulation from contaminated soils, and adulteration during processing and preparation [149, 156, 157]. While Pb concentrations in plant-based foods in the USA are usually low, this route of exposure is particularly relevant for children under 5 years, as Pb contamination has been found in some formulas, infant toddler cereal, cocoa powder and chocolate products, and candy ingredients and wrappers [20, 158–160]. Preparation of

baby formula with contaminated tap water also contributes to this burden of exposure [149]. Soil and dust ingestion of Pb is particularly relevant for young children because of the high ingestion rate related to repetitive mouthing behavior and hand contamination [161–166]. Consumption of fish and shellfish captured in water with high Pb contamination is also a relevant source [149]. The burden of exposure is higher for populations living in urban areas and those close to sites with Pb emissions (e.g., smelters, Pb battery recycling plants, and mines) and accumulation from other industrial activities. In the USA, the reference value for blood Pb in children was updated to 3.5 ug/dL in 2021 [167]. However, no safe level of blood Pb for human health has been identified [168].

Absorption, Biotransformation, and Elimination—The absorption rate from inhalation of inorganic Pb is almost 100% for small particles (< 2.5 μm) [149]. The absorption rate in the GI tract is variable. Adults absorb between 3 to 10% of ingested Pb, while children can absorb up to 50% [169–172]. Fasting status [146, 169–171, 173–175] and iron deficiency [176, 177] contribute to higher Pb absorption [178, 179]. Dermal absorption has been documented in animal models, but its contribution to body burden is minimal [149]. In the bloodstream, 99% of Pb enters red blood cells where it binds to various proteins [149]. Sigma-aminolaevulinic acid dehydratase (ALAD) has the highest affinity for Pb; the binding of Pb displaces zinc from this protein, impairing its function [20, 180]. The majority of lead is transported from blood into bone tissue, which accumulates 90% of the body burden. In the bone, Pb can replace calcium and bind phosphate, forming stable complexes that substitute the original calcium-phosphate salts within the bone matrix [181]. The accumulation of Pb in the bone is age-dependent and occurs mostly in areas that are undergoing calcification and remodeling at the time of exposure [182]. As a result, Pb primarily accumulates

in the trabecular bone of children and in cortical and trabecular bone in adults, where it can remain for more than 30 years [183]. From the bone, Pb can be transported back into the bloodstream and into other tissues when bone is resorbed [20]. Physiological and pathological processes that increase bone resorption, including pregnancy, menopause, pronounced weight loss, and osteoporosis, increase Pb concentrations in blood [20, 149, 184–189]. Organic Pb is metabolized in the liver where it undergoes oxidative dealkylation by P-450 enzymes. The main elimination routes are urine and feces, although excretion is very low [149]. Lead can also be eliminated in smaller proportions through sweat, saliva, hair, nails, and seminal fluids [190–198]. Lead can cross the placenta and is excreted in human milk, resulting in potential sources of Pb exposure during vulnerable developmental windows [199, 200].

Biomarkers—Total Pb can be measured in blood, bone, teeth, nails, hair, and urine [201, 202]. Whole blood Pb is the most used biomarker for recent and long-term exposures. If exposures are constant, one spot measurement of blood lead can be a reasonable indicator of long-term exposure [20, 149]. Although only 2% of the body burden of Pb is stored in blood [149], there is a constant recirculation of Pb from bone into the bloodstream. Blood Pb therefore reflects an integrated mixture of exposure from the past few months and has a longer-term exposure component over the years [20, 203]. However, short-term changes in

exposure can rapidly influence blood levels of Pb. To understand the burden of chronic Pb exposure, the cumulative blood Pb index (CBLI) can be calculated [149]. This index is based on repeated blood samples over time and provides an integrated measurement of average blood Pb levels over that time period [20, 201, 204–212]. Lead can be measured in bone tissue using noninvasive procedures such as K-Shell and L-Shell X-ray fluorescence (XRF) [213–215]. This is a biomarker of cumulative exposure since the primary reservoir of Pb in the body is bone. Accumulation of Pb in trabecular bone is preferably measured in the patella, calcaneus, and sternum; Pb in cortical bone is measured in the tibia, phalanx, or ulna [149]. Previous studies have reported high correlations between bone Pb measured by XRF and CBLI [20, 208]. However, this biomarker has important limitations, as several factors, including bone mass, body mass index, gender, age, and inter-laboratory variability may affect its accuracy [216]. Furthermore, even at low doses, XRF involves the use of radiation [182]. Chelatable Pb, which is measured using chelating agents such as dimercaptosuccinic acid (DMSA) and ethylenedi-aminetetraacetic acid (EDTA) administered prior to urine collection, is considered a biomarker of bioavailable Pb stores and Pb body burden. Chelation with EDTA requires intravenous administration [217, 218]. The best time for measuring chelatable Pb is 3–4 h after administering the chelating agent [219].

Several laboratory techniques have been developed over the past decades to allow the measurement of Pb and other metals in teeth dentine and enamel [220–223]. Teeth are a minimally invasive biomarker that can provide chronological information on cumulative exposure across the life course. Deciduous teeth can be used to assess exposures during the prenatal period and childhood [224, 125, 226]. Previous studies in children have reported strong correlations between dentine Pb and blood Pb concentrations (Spearman's $p = 0.64$, $p < 0.0001$) and cord blood Pb (Spearman's $p = 0.69$, $p < 0.0001$) [225, 227] [149] Placental Pb correlates well with maternal blood Pb [30, 228] and with Pb concentrations in drinking water [228]. However, similar to Cd, correlations between placental Pb and concentrations in cord blood have been inconsistent [229]. Hair, nails, urine, and plasma are not established biomarkers for measuring the internal dose of Pb; previous studies have reported low correlations between environmental Pb exposure, bone Pb, and Pb concentrations in these biospecimens, particularly at lower concentrations, therefore the potential exposure windows reflected by these biomarkers remain unclear [20, 230]. Urine and plasma Pb may be acceptable among populations exposed occupationally or at higher levels [230]. However, their utility for general populations is unclear.

Mercury

Major Sources of Exposure—Mercury can be found naturally in the environment as a result of volcanic activity and corrosion of rocks containing Hg [231, 232]. However, environmental contamination and resulting exposure to Hg occurs mostly due to anthropogenic activities, such as mining and smelting, coal combustion in thermal power plants, waste burning, and bioaccumulation of Hg in the food chain [233–236].

Mercury is found in several chemical forms. Humans are predominantly exposed to organic Hg (e.g., methylmercury) [237, 238], which can be found in seafood, poultry, a variety of pesticides, insecticides, thimerosal-containing vaccines, and in some herbal supplements

and alternative medicines [239]. Plants can also bioaccumulate organic Hg from soil [240, 241]. Inorganic Hg (Hg + 2) is used as an additive in some prescription drugs, such as laxatives or diuretics, and other products including teeth powdering and certain cosmetics [237]. Inorganic Hg can also be an intermediate product of metabolized organic Hg [242]. Metallic Hg (Hg0, also known as elemental Hg), which is the only metal found in a liquid state at room temperature, has been used in dental amalgams in the past, [243, 244], as well as in thermometers and as an additive to paint and other materials [237, 245]. Metallic Hg evaporates easily, contributing to human exposure through inhalation [235].

The main route of Hg exposure in the general population is oral ingestion from diet [246]. Fish consumption, which contains high levels of organic Hg, contributes to more than 90% of Hg exposure in the US [247]. Recent studies in populations that consume large quantities of rice have shown that Hg-contaminated rice may also contribute to exposure [248, 249]. Direct contact with metallic Hg used in medical equipment such as dental amalgams is a secondary route of exposure which occurs through inhalation of metallic Hg as a vapor [250]. Some cosmetic products like skin-lightening and whitening cosmetics may contain small amounts of inorganic Hg and constitute an additional source of exposure [251, 252]. The most relevant occupational exposures occur in metal and waste processing plants, manufacturers of electrical equipment and building materials, and medical professions, including dentists and other healthcare providers [236, 253, 254].

Absorption, Biotransformation, and Elimination—Organic Hg has the highest bioavailability of the three forms, being easily absorbed in the GI tract, with absorption via oral intake ranging between 50 and 100%. The absorption of metallic and inorganic Hg in the GI tract is minimal; however, more than 80% of inhaled metallic Hg is absorbed in the lungs entering the systemic blood circulation [255]. The organic and metallic forms of Hg can easily cross the blood–brain barrier, entering the central nervous system, which is a relevant target of Hg toxicity [256]. After absorption, both organic and inorganic Hg undergo a series of oxidation–reduction cycles [246]. Metallic Hg (Hg0) is mostly transformed into inorganic Hg in the bloodstream, where it enters red blood cells and it is oxidized to inorganic Hg (Hg + 2) by catalase enzymes [257]. This process also occurs in the lungs, the brain, and the liver [246, 258], and can be inhibited by substances such as ethanol, which can impair Hg uptake by red blood cells [259]. The metallic Hg that is not transformed into inorganic Hg is mostly eliminated through exhaled air in the lungs [246]. The main routes of elimination for organic Hg are the feces, followed by urine and hair; biliary elimination plays a particularly important role in the elimination of organic Hg and urinary excretion accounts for less than one-third of organic Hg elimination from the body. The half-life of organic Hg in blood ranges from 50 to 100 days. Hair mercury can reflect the levels of organic mercury in blood during the previous 100 days, with every cm of hair reflecting exposure during the previous month [246, 260, 261]. Inorganic Hg has a terminal half-life of approximately 1–3 months in the body [262]. The majority of organic and inorganic Hg forms accumulate in the kidneys and the brain, which are the main targets of Hg toxicity. The primary route of elimination for inorganic Hg is urine. The Hg urine elimination rate is representative of the overall body elimination rate of inorganic Hg [246]. Acute exposure to inorganic Hg has been shown to be followed by two elimination phases:

an initial phase of rapid elimination of high Hg concentrations from tissues (4–5 days) [246, 263] followed by a slower phase that can be prolonged due to persistent accumulation of Hg in tissues such as the brain which can last for years [264]. Both inorganic and organic Hg can be excreted in human milk [265, 266]. Mercury levels in cord blood are higher than in maternal blood, indicating placental transfer of Hg [267, 268].

Biomarkers—Mercury can be measured in several biospecimens, with urine, hair, and blood being used most frequently [246]. It can also be measured in feces, human milk, nails, and placenta [269, 270]. The different chemical forms of Hg have implications for its distribution, toxicity, accumulation, and elimination. As a result, different biospecimens reflect exposure to certain forms of Hg more accurately than others [250]. Hair is the biomarker of choice for measuring chronic exposure to organic Hg, as keratin binds to organic Hg [271, 272] Fingernails and toenails similarly reflect organic Hg for the same reason. Clippings from all ten toenails reflect exposure over the previous 6 to 12 months [273]. Prior studies have shown a high correlation between hair concentrations of Hg and brain tissue and whole blood at a ratio of 250:5:1. This ratio is recommended by the WHO for converting hair Hg concentrations to blood Hg concentrations [274]. Similarly, high correlations between nail and hair Hg ($r > 0.9$, $p < 0.05$) [273] and dietary Hg (Spearman's $p = 0.48$, $p < 0.01$)[275] have been reported. Hair is not a good biomarker for measuring the burden of exposure to metallic Hg (Hg0). To understand the distribution of Hg species (organic vs. metallic) in hair samples, measuring Hg-stable isotopic signature has been successfully used in previous studies [276].

During pregnancy, organic Hg concentrations in hair are highly correlated with fetal blood levels, indicating that it is a good biomarker for prenatal exposure [269]. Maternal nails collected in early pregnancy and at delivery are useful biomarkers of prenatal exposure to organic Hg over the previous ~ 3 months. Prior studies identified a high correlation between maternal nail Hg at parturition and hair segments at 0–3 cm from the scalp [273]. The utility of placental Hg as a biomarker may depend on the specific Hg species evaluated. A study in Sweden which measured inorganic Hg in the placenta and maternal blood and collected information on the number of dental amalgams reported moderate correlations with inorganic Hg in cord blood [277]. The same study also reported positive correlations between placental methylHg and concentrations in both maternal and cord blood and freshwater fish consumption. However, results have been less consistent for total Hg [30, 145, 148].

Urine Hg is considered the biomarker of choice for measuring exposure to inorganic Hg, both for the general population and for capturing occupational exposures [246]. Urine excretion reflects the internal dose of inorganic Hg accumulation in the kidney after acute exposure [274, 278], but also can be used as a measure of internal dose in chronically exposed populations [250]. Urine Hg can reflect exposure to inorganic Hg as well as to organic Hg that is de-methylated and excreted through the kidney. However, the proportion of organic Hg that gets demethylated and excreted in the urine remains unclear as previous studies have reported mixed findings [246, 279–282]. Blood reflects exposure to all chemical forms of Hg [250, 272, 283]. Organic Hg primarily accumulates in red blood cells where it binds to hemoglobin, whereas inorganic Hg is distributed between both red

blood cells and plasma [283]. The half-life of Hg in blood is approximately 50 days [284]. As a result, blood Hg is a reliable biomarker of recent exposure, although it can also be used as a biomarker of long-term exposure in populations chronically exposed to this metal. Maternal blood Hg concentrations during pregnancy can be used as a biomarker of prenatal exposure [269].

Nickel

Major Sources of Exposure—Nickel is found in soil, dust, and the atmosphere as a result of natural emissions. Anthropogenic sources of Ni include waste burning, combustion of fossil fuels, and steel production, among others, which also results in soil, water, and air contamination [285]. Nickel is also used as an alloy compound in jewelry, coins, and stainless steel materials and in other industrial activities such as fabrication of electric appliances and batteries [286].

Diet is the main route of exposure to Ni, as Ni can bioaccumulate in plant species that grow in contaminated soils [287], followed by inhalation and dermal contact [288]. Certain vegetables, such as spinach, asparagus, carrots, broccoli and green beans, tomato, cocoa, chocolate, and nuts can contain high concentrations of Ni [287, 289]. Smoking also constitutes a source of exposure [287, 290]. Populations that live near refineries and industrial sources of Ni are at higher risk of exposure [291]. Similar to other metals, household dust contamination with Ni is of particular concern for children [292]. In recent years, there is also concern about the use of metallic coils which contain Ni (nichrome) as an additional exposure among users of e-cigarette devices [293, 294].

Absorption, Biotransformation, and Elimination—The absorption rate of ingested Ni is highly variable and ranges from 2 to 30% [285, 286]. Approximately 20 to 35% of inhaled Ni is absorbed in the lungs. The solubility of Ni compounds has an impact on their absorption through cell membranes [288, 295]. While soluble Ni compounds tend to be easily absorbed by diffusion or transported by calcium channels or divalent cation transporters, insoluble particles can only be absorbed by phagocytosis [296, 297]. Fasting status and iron deficiency may also increase Ni absorption [286, 298] in the GI tract. Dermal absorption is generally low because little ionized Ni crosses the skin barrier [299]. This absorption increases with skin abrasions and can be relevant in occupational settings, particularly those where Ni nanoparticles are manipulated [300]. Dermal contact also leads to symptoms of contact dermatitis in 10–20% of the population [286]. In the bloodstream, Ni primarily binds to albumin, but also can be found in combination with amino acids and peptides [300]. The main elimination pathways for all sources of Ni exposure are urine and feces [285], and its half-life and accumulation in the body is relatively short, from 12 to 48 h [286, 301]. Nickel primarily accumulates in the lungs and the kidney, but can also accumulate in the heart, diaphragm, and spinal cord [302]. Magnesium and zinc can accelerate the elimination rate of Ni and decrease its systemic accumulation [303]. Cadmium and chromium can interact synergistically with Ni, increasing its toxicity [304, 305]. The use of chelation agents such as triethylenetetramine (TETA) and Cyclam, have been used to treat Ni toxicity successfully [286]. Nickel is also chelated by EDTA [306].

Biomarkers—As soluble Ni compounds are more likely to be absorbed, serum and plasma Ni reflect exposure to soluble Ni compounds most accurately [286]. However, Ni can also be measured in urine, feces, serum, and hair, which are the biomarkers of choice to assess exposure and internal dose [307]. High correlations between exposure to Ni and urine and serum Ni concentrations have been reported in several occupational studies [308–311]. Serum and urine Ni reflect short-term exposures, over the past 24–48 h [307]. Population levels of Ni in serum and urine are estimated to range from 0.2 and 1–3 μg/L, respectively. Whole blood is not a good biomarker of Ni [312]. Ni can accumulate in the placental tissue [313]. However, to our knowledge, no studies have investigated relationships between placental concentrations of Ni and more established biomarkers.

Tin

Major Sources of Exposure—Tin can be found in its divalent (Sn 2 +) or tetravalent form (Sn + 4) in soil, rocks, and water. Tin is used in several industrial activities in its inorganic form, including the production of glass, paints, perfumes and cosmetics production and food packages. Tin may also form organic compounds, such as tributyltin or triphenyltin, among others [314]. Organotin compounds are used as heat stabilizers, agrochemicals, and antifouling paints [314, 315]. The use of tributyltin in boat paints is a contamination source for marine ecosystems and its potential bioaccumulation in fish could be a source of exposure to Sn in the diet [315]. Tin is used in e-cigarette soldered joints and has been documented in e-cigarette aerosols [293, 316]. The main routes of exposure to Sn are oral ingestion, inhalation, and dermal contact [314, 317]. In the general population, ingestion of contaminated water [318], food, and beverages [319, 320] is the major source of exposure. Tin-lined cans, widely used in food packages, constitute a relevant dietary source. Populations with higher canned food consumption have a higher body burden of inorganic Sn [314, 321]. Similarly, marine food contributes to a relevant burden of exposure to organic Sn, as high levels of these compounds have been reported in the blood of individuals with high fish intake [322, 323]. It is estimated that ~ 90% of the US population has detectable levels of Sn in urine [324]. Dermal contact is most relevant in occupational settings [314].

Absorption, Biotransformation, and Elimination—After absorption, the majority of Sn is distributed from the blood stream into soft tissues and bone. The half-life of Sn in blood and soft tissue ranges from 1 to 3 days in animal models [314], compared with 2–3 months for bone [314].

The main route of elimination for both inorganic and organic Sn is urine [314], although a biliary route of elimination has been described as well [325]. There is limited data on the absorption kinetics, mechanisms of action, and measurement of Sn body burden in humans.

Biomarkers—Tin levels can be estimated in blood, urine, soft tissues, and bone. Inorganic Sn is usually measured in biological specimens, as the measurement of organic Sn requires sampling speciation for specific organic forms (e.g., alkyltin compounds) and their metabolites. Blood Sn is a biomarker of recent exposure to inorganic Sn within the previous 2 to 15 days [314]. Inorganic Sn accumulates in bone for an estimated period of 2–3 months [314]. However, only invasive techniques are available for measuring bone Sn,

which limits its practical applicability. Urinary measurement of both inorganic and organic Sn is a good biomarker of exposure, as urine is the main route of elimination. Urine samples can be digested with acid to eliminate organic matter and then oxidized to extract Sn(+4). Measurements of inorganic Sn in urine can be used as a marker of exposure in human studies [326]. The collection of urine in plastic tubes compared to glass vials can reduce the ability of measuring organic Sn species by 70% [326].

Uranium

There are three main forms of U: natural U, enriched U, and depleted U [327, 328]. Their chemical properties, however, including chemical toxicity, are identical [328]. Radioactivity in U takes thousands of years to naturally decay, which gives this element an extremely long halflife [328]. For this section, we will focus on the chemical toxicity of natural U, as radiation effects are outside the scope of this review.

Major Sources of Exposure—Uranium is a component of rocks and soil and can occur naturally in groundwater. Uranium can also undergo oxidation–reduction reactions and combine with organic compounds in the environment. The mining of U-containing rocks for nuclear fuel and the production of phosphate fertilizers, which are also a source of Cd [329, 330], are the main anthropogenic sources of U [331–335]. These activities can result in contamination of soil, water, and air with U [334]. The main routes of exposure to U in the general population are through drinking water and diet [336]. Drinking water contamination with U is particularly relevant in the Western US, where the leaching from abandoned mines into the water systems disproportionately affects American Indian communities [337–339].

Uranium can be adsorbed from the soil into the roots of plants, while the reported bioaccumulation rates in plants and fish are low, tubercules and root vegetables can adsorb U on its surface [340]. The daily dietary intake of U is estimated to range between 1 and 20 μg [341, 342]. Dermal absorption and inhalation [343, 344] absorption can occur as well. Inhalation is the main route of exposure in occupational settings such as mines, and dermal exposure is notable in military personal [345]. Occupational exposure can occur in workers involved in U mining and milling and individuals working with U weapons and phosphate fertilizers, as well as populations working and living close to fossil fuel plants [336].

Absorption, Biotransformation, and Elimination—The toxicity of U depends on its solubility, particle size, and exposure duration [346]. Water-soluble U compounds (e.g., hexavalent U, uranyl nitrate, uranyl fluoride) are more toxic than those with low solubility (e.g., tetravalent U, sodium diuranate). Insoluble U compounds mostly exhibit toxicity when they are inhaled directly into the lungs, where they can accumulate [328].

Bioavailability and absorption are low in all routes of exposure. The absorption in the GI tract ranges from 0.1 to 6%, depending on the solubility of the ingested compound [347]. The absorption rate through inhalation is also low and ranges from 0.2 to 5% [348]. Overall, previous population studies have documented an absorption rate of less than 2% [349–351]. Fasting status and low-iron diet have been shown to increase absorption [347]. Some studies hypothesize that the DMT1 transporter may be involved in U absorption in the GI tract [347], but no studies have demonstrated this.

From the bloodstream, U is mostly distributed into bone, kidneys, and liver [331], with bone tissue accumulating most of the body burden [352, 353]. In animal models, U has been shown to cross the placenta [327]. The half-life of U is estimated to be 70–200 days in the bone and between 2 to 6 days in the kidney. Uranium usually undergoes some metabolic transformations, including the oxidation of tetravalent U to hexavalent U then a uranyl ion. Uranium compounds have high affinity for proteins in plasma, mostly transferrin, and the proximal tubule where they tend to bind [354–357]. For absorbed U, urine is the main route of elimination; it is estimated that more than 70% of the body U is filtered by the kidney [342], which is the main target organ for toxicity [358, 359]. A study in veterans exposed to high doses of U was able to document U in urine up to 7 years after exposure concluded [360]. Other elimination routes include feces, sweat, and exhaled breath. The main route of elimination for non-absorbed U is feces.

Biomarkers—Uranium can be measured in urine, feces, nails, hair [361–364], bone, and soft tissues. Total urinary U, including the determination of U isotopes, is the biomarker of choice for exposure [328]. Urine U is considered a good biomarker from all sources of exposure, as kidney filtration is the main route of elimination for this chemical [346, 354, 365–371]. Urinary U is representative of exposure over the past 2 weeks, one spot measurement can be used as an indicator of chronic exposure in populations with constant exposures [360, 372–374]. Previous studies have reported a high correlation between urine U and environmental U in air, water, and food in chronically exposed populations [375]. For every 1 μg/dL intake of U, an increase of 2.06 ng/dL, 37 ng/g, and 0.05 ng/g of this compound is expected in urine, hair, and nails respectively [363]. Hair and nail U are positively correlated, and increasing evidence suggests that both may reflect exposure from the previous weeks to months; however, more studies are needed to establish these measures as biomarkers of exposure [376]. The determination of hair U requires sample decontamination [364]. Uranium also be measured in bone and soft tissues, as it distributes within these organs in the body; previous studies have reported a significant association between water and bone U in adult men [377]. However, noninvasive methods for the assessment of U in bone tissue are not available, which is a major limitation [377].

Essential Metals

Table 2 includes a summary of the most frequently used biomarkers, sample sources, their half-lives, and other considerations for the essential metals included in this review. Essential metals have several physiological functions in the human body. Essential metals are tightly regulated in the body by metabolic mechanisms to guarantee their availability for cellular functions. Both low and high levels of essential metals are associated with adverse health effects. However, while the health impacts of essential metal deficiencies are well characterized, there is still a need to further assess the impact of excessive levels of essential metals on human health.

Manganese

Manganese is an essential element, which plays important roles in bone and cartilage formation as well as wound healing [378, 379]. At the molecular level, Mn is a cofactor for several enzymes (e.g., glutamine synthetase) and is involved in developmental, reproductive,

immune, and energy production processes including glucose metabolism and mitochondrial function [380]. However, at elevated levels, Mn can exhibit neurotoxic effects [381].

Major Sources of Exposure—Manganese is usually found in combination with other elements, forming oxides, carbonates, or silicates [382]. The most frequent metallic forms are Mn (+ 2) and Mn (+ 3) [380]. Due to its chemical properties, Mn is used in several industrial processes including batteries, steel, cosmetics, leather, glass, and ceramics manufacturing. Gas and fossil fuel combustion can lead to the emission of Mn phosphate [383]. This compound is also used as an additive to pesticides and fungicides in agriculture. Recently, it has been proposed as a "less toxic" alternative contrast agent to gadolinium in medical procedures such as magnetic resonance imaging (MRI) [384, 385], and it is commonly added to parenteral nutrition preparations for children [386]. The main route of exposure to Mn in the general population is ingestion through diet and water. The mean daily Mn intake in the diet is estimated to range between 0.7 to 10.9 mg/day [383, 387]. Foods with high-Mn concentrations include rice, nuts, whole grains, and legumes. Tea, chocolate, and some seafoods have high levels of Mn as well. The mean intake of Mn from drinking water is estimated to be around 0.02 mg/day [387]. However, some populations, such as private well users in the US, may be exposed to higher levels [388]. Inhalation can be the main route of exposure to Mn in the occupational setting [380], particularly for miners, welders, and smelter workers [389, 390].

Absorption, Biotransformation, and Elimination—The absorption rate of Mn in the GI tract is estimated to range from 3 to 5% [391]. Mn can be absorbed by passive diffusion or by transporters including DMT1, which is used by other divalent cations, such as iron and calcium [392]. As a result, higher Mn absorption rates have been documented in iron-deficient populations due to the overexpression of DMT1 transporters [393, 394]. Absorption rates are higher in women compared with men, which may be influenced by iron status [395], and in children compared with adults [396]. Similar to iron, high dietary calcium intake has an antagonistic effect on Mn absorption [397].

Inhaled Mn can enter the bloodstream from the lungs or be transported directly from the olfactory bulb into the brain [398, 398–400]. From the bloodstream, Mn is distributed and accumulated in the liver, the pancreas, the bone tissue, the kidneys, and the brain [401–403]. Blood Mn levels are tightly regulated. Mn has a high affinity for proteins, including albumin and transferrin [404], as well as transporters such as DMT1, found in the red blood cells [405]. Endogenously, Mn is mostly found in its divalent and trivalent oxidation forms, which can undergo oxidation and reduction reactions. The liver is responsible for Mn conjugation into the bile, which leads to its excretion in the feces, the main route of elimination [380, 391]. Mn can also be eliminated in urine and sweat [406] and has been documented in human milk [407–411]. Studies using animal models have reported that the half-life of Mn ranges from 5 to 74 days in the brain and up to 690 days in bone [412–414]. For humans, the estimated average half-life of Mn for bone is 9 years [415]. Mn can accumulate and cross the placenta, and both high and low Mn exposures during the prenatal period have been associated with adverse health outcomes and DNA methylation changes in the offspring [416, 417].

Biomarkers—Urine and blood are the most frequently used biomarkers of Mn exposure. However, they present several limitations. Studies examining the correlation between environmental Mn and its concentrations in blood and urine have been heterogeneous. While some occupational studies found high correlations between dust or airborne Mn with blood Mn in groups of workers [400, 408, 418–421], findings among non-occupationally exposed individuals have been inconclusive [408, 419, 420, 422, 423]. Mn in the bloodstream is rapidly cleared through the liver and excreted into the bile and therefore has a short half-life in blood [424]. Blood Mn has a high intra-individual variability, which limits its sensitivity as a biomarker. As urine is a minor elimination pathway for Mn, its usefulness as a biomarker of exposure is limited [425–427]. Mn can also be assessed in other biological assays including feces, hair, nails, saliva, teeth, bone, and cerebrospinal fluid. Hair Mn correlates well ($r = 0.48$) with environmental Mn exposure from drinking water [428]. It has been proposed as a biomarker of exposure within the previous months and it is considered the best biomarker of exposure in children [428–431]. However, hair requires decontamination, and Mn concentrations can vary with hair color, as Mn has a high affinity for pigments [432]. Water Mn at concentrations exceeding 9.8 μg/L has a moderate correlation with toenail Mn ($r = 0.38$), suggesting the possible use of nail Mn as a biomarker of moderate to high Mn exposure [433]. Imaging diagnostic techniques such as MRI also allows for the identification of Mn accumulation in the brain [434]. Animal models have shown a high correlation between Mn concentrations in teeth and blood ($r = 0.69$, $p < 0.001$) and also between teeth and bone ($r = 0.76$, $p < 0.001$) [432].

Molybdenum

Major Sources of Exposure—Molybdenum is an essential micronutrient for plants and animals that is widely present in soil and water, but can also be found in the atmosphere. It is typically present as a mineral forming molybdenite, ferrimolybdenite, and jordisite [435, 436], and as isopolyanions such as molybdate, which form Mo salts. Mo has 5 oxidation states, with Mo (IV) and Mo (VI) being the most common. The environmental pH has an influence on this oxidation state, which determines Mo bioavailability and soil adsorption [437, 438]. Mo is widely used in industrial and mining activities, including metallurgical applications, followed by its use as a catalyst and as a pigment [439]. Some fertilizers also contain Mo salts [440]. Typically, it is used in combination with other metals such as chromium, Ni, Mn, tungsten, and cobalt, among others [441]. A radioactive isotope of Mo (99Mo) is used in nuclear medicine to conduct imaging scans [442] and can be a source of exposure to ionizing radiation in the hospital setting [435].

For the general population, the main route of exposure to Mn is ingestion from the diet. Leafy vegetables, grains, legumes such as beans, animal organs, and milk constitute the main sources of Mo in the diet [443]. Exposure from drinking water and air is relevant in mining and industrial occupational settings, as well as for populations living near contaminated areas [441]. Mo has also been found to cooccur with As and tungsten in groundwater samples in Bangladesh [388, 444].

Biotransformation/elimination—The absorption of Mo in the GI tract is variable and strongly depends on the dose and its ingestion with other compounds. When ingested with

food, its bioavailability ranges from 20 to 60% [445]. Nevertheless, it goes up to 80–100% in experimental studies when stable isotopes were administered orally and intravenously to healthy volunteers [446–448]. Its transportation through the GI tract mucosa has not yet been elucidated, but anion transporters may be involved, according to animal models [446–448]. The absorption of inhaled Mo depends on particle size and solubility. Large particles are deposited in the bronchi and transported into the GI tract, and small particles can be directly absorbed from the alveoli into the bloodstream. Hexavalent Mo is the most soluble compound [436]. From the bloodstream, Mo is mostly distributed to the liver and the kidney, its main organs of accumulation [88, 449–455]. Mo can cross the placenta and be distributed to the fetus during pregnancy and it has been documented in human milk [456]. Mo can undergo oxidation and reduction processes after absorption. Physiologically, Mo in its molybdate oxidation form is incorporated into the cell where it binds to a molybdopterin and forms the enzymatic cofactor Moco (a sulfur-molybdate complex) [457–459], which plays a role in cell metabolism [460]. The main route of Mo elimination is through the kidney. Urine concentrates up to 90% of the absorbed dose of Mo from all routes of exposure. The presence of copper and sulfates accelerates Mo elimination by inhibiting its tubular reabsorption [461]. Biliary excretion is the second major route of elimination [457].

Biomarkers—Molybdenum can be measured in urine, blood, plasma, hair, and some tissues. Given that urine is the main route of Mo elimination, urinary Mo is a useful biomarker of exposure and is sensitive to changes in dietary Mo intake [445, 446, 448]. Plasma Mo has also been correlated with dietary intake. However, significant changes in plasma Mo only occur at high doses (> 460 μg/day). As a result, urine Mo is the preferred biomarker for assessing short-term exposure to this metal [379]. Blood Mo increases for a few hours after dietary intake; however, because the half-life is very short, blood Mo is not an established biomarker of exposure. Hair and toenails are not reliable biomarkers of Mo exposure as there is a high inter-laboratory variability. Additionally, their correlations with blood, urine, and dietary Mo exposures are low and the window of exposure they reflect is unclear [457, 462].

Selenium

Selenium is a metalloid and an essential micronutrient for humans. It is a fundamental component of selenoproteins, a family of 25 proteins all of which require the proteinogenic amino acid selenocysteine for their functionality [463]. Selenoproteins play a role in thyroid hormone metabolism, the immune system, antioxidant defense processes (e.g., glutathione peroxidase), and control of oxidation and reduction reactions intracellularly [464]. Despite its role as an essential nutrient, Se has a narrow safety margin, and excessive exposure to Se can cause adverse health effects [465, 466].

Major Sources of Exposure—Selenium is naturally found in rocks and soils and to a lesser extent in surface and groundwater [467]. Se can be found as inorganic Se mostly in soil and water in different oxidation states: as Se (+ 0), selenide (−2), which are insoluble metals, and as selenites (+ 4), and selenates (+ 6), which are soluble alkali. Organic Se compounds such as selenomethionine, selenocysteine, and dimethyl selenide are the most common sources of Se in food. The main anthropogenic sources of environmental Se are

the burning of coal and fossil fuels, mining, smelting, and agricultural activities, as well as the industrial production of photocells and glass [468, 469]. The main route of Se exposure for the general population is diet, with foods such as organ meat and seafood, cereals and grains, brazil nuts, and other unshelled nuts, generally being rich in Se [465]. Some dietary supplements also contain high levels of Se [470]. Plants and aquatic organisms can bioaccumulate Se from soil and water, incorporating it into the food chain. Runoff from agriculture, industrial waste, and sewage treatment plants can directly contaminate surface and ground water sources [468]. Se bioaccumulation strongly depends on the soil concentration, environmental pH and solubility of the Se species [471, 472].

Absorption, Biotransformation, and Elimination—In the GI tract, Se has a high bioavailability with absorption ranging from 55 to 90% [473]. The absorption rate can vary across inorganic and organic Se species [474]. Selenomethionine and selenocysteine are predominantly found in animal foods [475], while selenate and selenite are predominant in fish [476], and γ-glutamyl methylselenocysteine is predominant in plants that bioaccumulate Se [477]. However, the distribution of Se species in food needs to be further studied to understand its bioavailability [473, 478]. Once in the bloodstream, Se tends to bind to proteins such as albumin but is also transported as free species by mechanisms still under research [479]. The liver is the main organ where Se undergoes metabolism and distribution, transforming into selenoproteins that are then distributed to other tissues. From plasma, Se can also be absorbed by the kidney, the testis, and the brain [480, 481]. The main route of Se elimination is urinary excretion. Under physiological conditions, excess Se is mostly transformed into monomethylated Se, which is a selenosugar, and excreted into the urine [482]. Under high exposure conditions, Se is largely transformed into di- and tri-methylated Se and excreted into urine [483].

Biomarkers—Selenium can be measured in blood, urine, hair, nails and feces. Plasma Se is the biomarker of choice for Se status, with a half-life of a few days [484]. Plasma Se decreases with age and is generally lower in smokers, people with malnutrition, and during acute inflammatory processes, reflecting poor Se status [485]. Red blood cell Se is also a good biomarker of Se with a half-life of two months [20]. Selenoprotein P (the most abundant selenoprotein) has been proposed as biomarker of exposure within the previous 2 to 4 weeks, with heterogeneous findings among studies. While some studies in healthy children and adults have reported high correlations between Selenoprotein P in plasma and Se supplementation, Selenoprotein P levels can also increase due to other factors including age, body mass index, alcohol intake, and underlying comorbidities such as fatty liver disease [486–488]. Whole blood and serum Se correlate well with dietary Se intake ($r = 0.78$ and 0.74, respectively) [489]. Selenium is excreted in urine as a methylated product and its methylation status depends on Se body burden. Under conditions of low exposure and within its physiological range, the main product in urine is monomethylated Se, a selenosugar. However, under higher exposure conditions, Se is mostly methylated into di- and trimethylated forms. Measurement of the different methylated products in urine has been proposed as a possible excess and body burden indicator as their proportions vary with different exposure doses [483]. Toenail Se represents a good biomarker of past exposure ranging from the prior 6 months to a year. The correlation with dietary Se

intake is moderately high ($p = 0.67$) [489]. Hair Se, however, is subject to substantial contamination from hair products and is not considered an adequate biomarker of exposure [490, 491]. External contamination of hair Se is particularly relevant as Se is used as an active ingredient in anti-dandruff shampoo and hair growth serums [492, 493]. Maternal and cord blood Se correlate well with Se concentrations in the placenta [148, 494–496].

Zinc

Zinc is an essential nutrient [497], and is the second most abundant trace element in the body after iron [498]. Zn deficiency has been associated with impaired development [499] and deleterious effects in the central nervous system, fertility, wound healing, and immune function, among others [497]. Exposure to excess levels of Zn can have direct negative health effects on the lungs, cardiovascular, GI, and immune systems. The inhalation of Zn oxide is particularly toxic, leading to metal fume fever [500–502]. Increased Zn body burden can also interfere with the metabolism of other essential elements, including iron and copper [497].

Major Sources of Exposure—Zinc is commonly found in soil, air, surface, and groundwater, usually as a Zn oxide or forming sphalerite (ZnS) [497]. The main route of exposure to Zn in the general population is diet, with meat products and shellfish being major dietary sources of Zn [497, 503]. However, several anthropometric activities, including mining, smelting, electroplating, metallurgic operations, and the use of products that contain Zn as an additive (e.g., paints, rubber, alloys), contribute to Zn contamination [504–506]. Workers from those industries are particularly exposed to high levels of metallic Zn and Zn compounds primarily via inhalation [507]. Water and soil Zn concentrations are also high in industrial and mining areas, which constitutes an additional source of exposure for nearby populations [508].

Absorption, Biotransformation, and Elimination—Zinc can be absorbed by passive diffusion or mediated by transporters, with absorption rates of ingested Zn ranging from 20 to 30% [497]. The bioavailability of Zn in the GI tract is increased by citric acid and decreased by iron, calcium [509], phosphorus [497, 510], fiber, and phytate [511]. As a result, individuals with diets rich in vegetables have lower rates of Zn absorption. In the bloodstream, Zn binds to metalloproteins intracellularly in the red blood cells or travels in plasma, mostly bound to albumin and alpha-2 macroglobulin, which represents the active pool of Zn for metabolism [498]. Zinc is widely distributed within body tissues, with the musculoskeletal system accumulating 90% of the body burden [512], followed by the GI tract, brain, kidneys, heart, lungs, and pancreas [497, 501, 513–515]. Zinc primarily undergoes transformation and elimination in the liver. Zinc is mostly excreted in the bile [516, 517], where it can undergo enterohepatic circulation. The elimination rate in feces is 2–4 mg/ day. Urinary elimination accounts for a smaller fraction, with a net elimination rate of 0.5 mg/day [498]. Urinary excretion of Zn can increase in the presence of metabolic disorders, especially uncontrolled diabetes, in which case urinary Zn levels reflect impaired glucose metabolism rather than Zn exposure or status [518]. Zinc can also be eliminated through the skin and hair [519] and has been documented in human milk [520]. Evidence for

placental Zn is very limited, although weak positive correlations have been reported between placental Zn and maternal and cord blood Zn [148].

Biomarkers—Zinc can be measured in plasma, urine, nails, hair, and other biological fluids and tissues [497]. However, Zn is mostly distributed intracellularly in the musculoskeletal system and has a slow turnover, with the functional pool of Zn remaining under 10% of the body burden [521]. As a result, the use of any single biomarker may have limited validity [498] and there is a need for the development of highly sensitive biomarkers for Zn body burden. Zinc in plasma can be used as an indicator of recent exposure but the sensitivity and specificity are low [497]. Plasma Zn tends to increase after supplementation, although findings have not been consistent in previous experimental studies [521, 522]. Plasma Zn does not represent intracellular accumulation and it is only representative of 0.1% of the body burden [523] and should be interpreted carefully in situations when there is an expansion of plasma (e.g., during pregnancy [524] or after surgery), in situations of acute Zn deficiency [525], or in the presence of other comorbidities (such as diabetes) [526]. Adequate sample collection and processing for blood Zn is fundamental for its correct interpretation, as contact with gel separators, rubber, and heparin can lead to sample contamination and hemolysis which can artificially increase plasma Zn levels [527]. Urinary Zn can be used as a biomarker of recent exposure [527]. In contrast, whole blood Zn is nota good biomarker of changes in Zn exposure or depletion because the levels of Zn in red blood cells remain stable after supplementation or depletion [528, 529]. Additionally, nails and hair are not established biomarkers of Zn exposure, as their correlations with urine and blood Zn concentrations are low and the exposure window reflected is unclear [530, 531]. Given the limitations for most Zn biomarkers, assessment of dietary Zn intakes has been proposed as the best method for estimating Zn exposure [529, 532].

Discussion

In this review, we provide up-to-date knowledge of the strengths and limitations of biomarkers for 12 metals that are frequently used in multi-metal epidemiologic analyses and discuss major sources of exposure (Fig. 1) to aid metals researchers as they plan their analyses and interpret their results.

Recommendations

Key takeaways and recommendations for biospecimens are highlighted in Figs. 2 and 3, respectively. Understanding the major pathways of metal exposure is critical for making sound analytical decisions and interpretations. For metals such as As and Hg, it is important to consider, ideally before the analysis stage, whether it is sufficient to measure total As or total Hg without speciation. For example, if the study population regularly consumes seafood, the predominant As species in blood and urine will be arsenobetaine, which is non-toxic, rather than the toxic inorganic As species [68]. Thus, biomarkers which reflect total As may not represent the exposure of interest and may lead to inappropriate interpretations of results. For some populations, measurement of speciated arsenic may even be insufficient, as some organic arsenicals are metabolized to DMA, which is also the predominant metabolite of inorganic arsenic [70], adjustment for arsenobetaine levels can

be useful in these cases. Organic Hg species are also found in seafood [237–239]. Thus, if seafood consumption is common in the population, total Hg measures will primarily reflect organic Hg, which is the most toxic/neurotoxic species due to its ability to cross the blood–brain barrier, unless there is an additional source of exposure to consider. If organic Hg is of interest, and speciation is not an option, hair or toenails could be used [271–274]. Alternatively, if inorganic Hg is of interest, and seafood consumption is low in the study population, urinary Hg may be used as an appropriate biomarker [246, 250, 279]. There is no single biological matrix that is the best for all metals. For some metals, such as Pb, blood better reflects exposure than urine [20, 62, 68, 230, 246, 307, 326, 328, 361–364, 533]. However, for other metals, such as Ba and Mn, there is not yet an established biomarker that reliably reflects environmental exposure [76, 78, 108, 425–427, 534]. While most urinary markers reflect recent metal exposure, urinary Cd and Sn are exceptions, reflecting chronic exposure to these metals [130, 131]. Emerging biomarkers such as non-invasive XRF in bone allow for the assessment of chronic exposure to Pb and may help researchers overcome some of the limitations of blood Pb [208, 213–215, 225, 227]. Further, essential metals such as Mo and Zn are tightly regulated by homeostatic processes; thus, elevated levels in urine may reflect body loss and metabolic processes rather than excess exposure [445, 498]. These differences are important to keep in mind when interpreting results from multi-metal analyses.

In addition to understanding metal-specific exposure sources and analytical considerations, other important considerations when using a multi-metal approach include dilution adjustment (i.e., urinary creatinine, specific gravity), and adjustment by indicators of renal function (i.e., eGFR, serum creatinine) when using urine biomarkers [535, 536]. Growth rate, matrix-dependent factors, and environmental contamination when using nails and hair, as well as potential contamination from collection tubes and storage vials and the limits of detection of the analytical procedures.

When selecting biomarkers, it is also critical to consider the exposure window of interest. Chronic exposure to metals is typically most relevant, especially for populations exposed in the low-to-moderate range, yet many biomarkers reflect recent exposures. If metal exposures vary over time (e.g., due to fluctuations in diet, changes in the environment, implementation of regulatory policies), biomarkers that reflect integrated exposures over longer durations may be preferable. Toenails are attractive in this regard, and they seem to be reliable biomarkers of exposure for As, Hg, Mn, and Se [74, 376, 462]. However, for other metals such as Cd, Pb, or Ni, toenails seem to be inadequate or need additional study [376]. Toenail growth rate may also influence toenail metal concentrations and may therefore be an additional source of measurement error and bias. It is particularly important to consider the exposure window reflected by a biomarker when the goal is to identify vulnerable windows, such as critical periods of development. For example, while many metals can be measured in cord blood and the placenta, these biospecimens can only be collected non-invasively at birth and thus typically reflect exposures which occurred in late pregnancy. The collection of maternal biospecimens during pregnancy, such as blood and urine, or the postnatal collection of biospecimens that reflect long-term exposures, such as toenails, may therefore be more appropriate for capturing earlier windows in pregnancy. Deciduous teeth also hold promise as a unique tool for identifying susceptible windows of exposure in children, as metals

accumulate in primary teeth incrementally beginning in utero and can therefore be measured in distinct tooth layers, allowing for precise estimates of exposure timing [537, 538]. As a result, children's health cohorts which did not collect biospecimens during pregnancy or in early childhood can use deciduous teeth to retrospectively reconstruct metal exposures which occurred during the pre- and postnatal periods. Adult teeth are also increasingly being used to assess the burden of exposure over the previous years.

Conclusions

As a result of the unique biotransformation and elimination pathways of different metals, not all biomarkers are adequate measures of exposure. For example, whole blood is a good biomarker of As, Cd, Pb, Hg, and Sn exposure, but it is not a good indicator for Ba, Ni, or U. For essential metals, whole blood estimates have a challenging interpretation, as these metals are tightly regulated by physiological mechanisms. Urine is not a good biomarker of Pb exposure. Hair and nails are good biomarkers of exposure to As, organic Hg, U, and essential metals such as Mn and Se. However, they are not established biomarkers for Cd, Pb, Mo, or Zn This review aims to aid metals researchers in their analysis planning, analytical approaches, and interpretation of results. As metals epidemiology moves towards embracing a multimetal/mixtures approach and expanding metal panels to include less commonly researched metals, an in-depth understanding of metal biomarkers and their limitations is key for making sound analytical decisions and appropriately interpreting results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

As the manuscript is a narrative review, no data analysis was conducted and therefore, a data availability statement likely does not apply to this manuscript.

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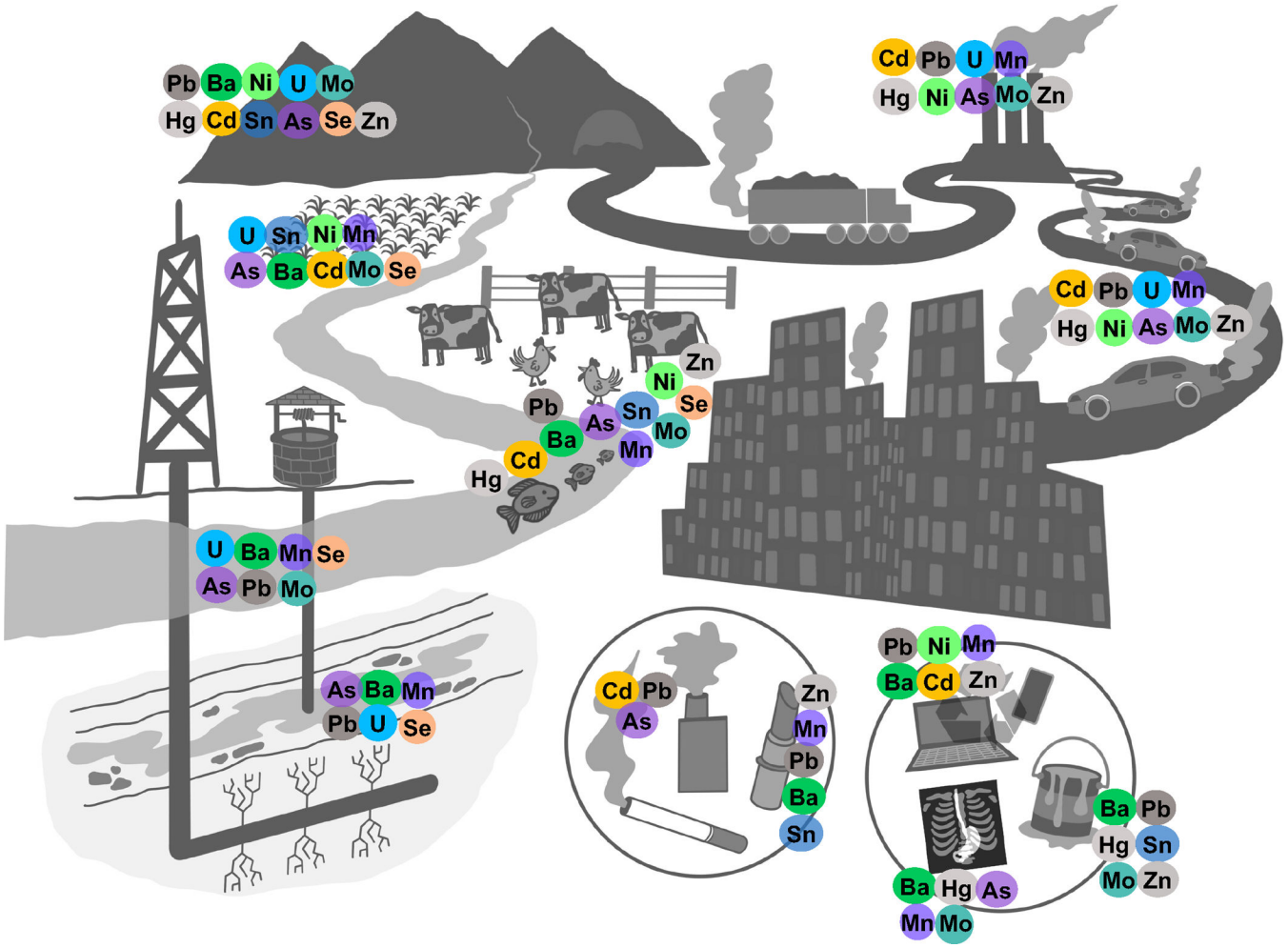

Figure 1. Graphic summary of the main sources of exposure for the metals included in the review.

- Not all biospecimens are adequate exposure biomarkers for all metals
- Identifying and using appropriate biomarkers is key when planning and conducting epidemiological studies on metals exposure
- Biomarkers reflect different periods of prior exposure depending on metal half-lives and exposure patterns
- Metals can interact with other molecules and other metals
- Understanding the biotransformation and elimination of individual metals is key to identifying the best biomarkers for exposure windows of interest
- Essential metals are tightly regulated in blood and plasma and often normally distributed
- Some essential metal biomarkers only reflect “excess” of exposure to metals beyond physiological levels

Figure 2. Key takeaways box.

- Urine biomarkers often use spot urine samples and require correction for urine dilution
- Urinary arsenic requires speciation and/or adjustment for arsebonetaine in most populations, particularly when seafood intake is common
- Urine is not a good biomarker for lead exposure
- Different biomarkers are required for evaluating inorganic versus organic mercury
- Placenta, toenails, and fingernails are emerging biomarkers of exposure; however, they have limitations for some metals
- Methods development still needed to account for differences in tissue growth rate and other matrix factors that affect hair and nails

Figure 3. Key takeaways for biospecimens.

Table 1.

Summary of the most commonly used biomarkers for non-essential metals, their timing and important considerations when including in a study.

Timing is divided into 4 categories according to the half-lives of the biomarkers in the body: Acute (1–3 days prior), Recent (up to 1 month prior), Sub-Chronic (1 to 6 months prior), Chronic (>6 months prior).

Metal	Biomarker	Timing[c]	Established Biomarker	Considerations
Arsenic	Whole Blood	Recent	Yes	Requires speciation of metabolites to aid assessment of toxicity Has analytic limitations
	Urine[a]	Recent	Yes	Requires speciation of metabolites to aid assessment of toxicity
	Hair[b]	Sub-Chronic		Validated protocols for sample processing are needed. High interindividual variability in growth rate Predominantly reflect inorganic As
	Toenail/Fingernail[b]	Sub-Chronic/ Chronic	Yes	
	Placenta	Sub-Chronic	Unclear	Limited studies
Barium	Urine[a]	Acute	Yes	Limited studies
	Feces	Recent	Unclear	Limited studies
Cadmium	Whole Blood	Recent and Sub-Chronic	Yes	Reflects ongoing and short-term exposure but has a long-term component too
	Red Blood Cells	Recent and Sub-Chronic	Yes	Reflects exposure over past 100 days. Similar half-life as whole blood
	Urine[a]	Chronic	Yes	Reflects long-term exposure Low intraindividual variability Renal injury can limit validity
	Hair[b]	Unclear	No	Window of exposure relfected is unclear
	Toenail/Fingernail[b]	Unclear	No	Window of exposure relfected is unclear
	Placenta	Sub-Chronic	Unclear	Correlates well with maternal blood and urinary Cd
	Feces	Recent	Unclear	Captures dietary intake
	Liver/Kidney	Chronic	Unclear	Low sensitivity Reserved for occupational biomonitoring
Lead	Whole Blood	Recent	Yes	Good indicator in low exposed populations
	Cumulative Blood Lead Index	Chronic	Yes	Integrated measurement of average blood Pb levels over time
	Urine	Unclear	No	Not a good biomarker
	Hair[b]	Unclear	No	Window of exposure relfected is unclear
	Toenail/Fingernail[b]	Unclear	No	Window of exposure relfected is unclear
	Placenta	Sub-Chronic	Unclear	Correlates well with maternal blood concentrations, inconsistent findings for cord blood
	Bone	Chronic	Yes	Non-invasive Intra-individual and inter-laboratory variability
	Teeth	Chronic	Yes	Decidious and adult teeth reflect different windows of exposure.
	Chelatable urine	Chronic		Requires intravenous EDTA
Mercury	Whole Blood	Recent	Yes	Indicator of total mercury, but mostly organic mercury in populations with seafood intake

Metal	Biomarker	Timing[c]	Established Biomarker	Considerations
				Valid as measurement of internal dose in chronically exposed populations Indicator of pre-natal exposure in maternal blood
	Red Blood Cells	Sub-Chronic	Yes	Indicator of organic mercury
	Urine	Recent	Yes	Indicator of inorganic mercury Represents internal dose in chronically exposed populations Can also reflect demethylated organic mercury
	Hair[b]	Chronic	Yes	Indicator of organic mercury Indicator of pre-natal exposure (maternal hair)
	Toenail/Fingernail[b]	Sub-Chronic	Yes	Indicator of organic mercury
	Placenta	Sub-Chronic	Unclear	Emerging biomarker
Nickel	Plasma/Serum	Acute	Yes	Reflect exposure to soluble Ni compounds
	Urine	Acute	Yes	High correlation with serum Ni
Tin	Whole Blood	Recent	Yes	Speciation needed for organic forms
	Urine	Chronic	Yes	Indicator of inorganic tin, after digestion with acid and oxidation, extracting (Sn+4)
	Bone	Chronic	Unclear	Only invasive techniques available
Uranium	Urine	Acute and Recent	Yes	Uranium isotopes can be determined Can reflect chronic exposure if exposure is constant
	Hair[b]	Sub-Chronic	Unclear	High correlation with nail U
	Toenail/Fingernail[b]	Sub-Chronic	Unclear	High correlation with hair U
	Bone and soft tissue	Chronic	Unclear	Only invasive techniques available

[a] Needs adjustment for urine dilution (creatinine or specific gravity)

[b] Sample requires environmental decontamination

[c] Timing refers to the exposure window that the biomarker reflects relative to sample collection.

Table 2.

Summary of the most commonly used biomarkers for essential metals, their timing and important considerations when including in a study.

Timing is divided into 4 categories according to the half-lives of the biomarkers in the body: Acute (1–3 days), Recent (up to 1 month), Sub-Chronic (1 to 6 months), Chronic (>6 months).

Essential Metal	Biomarker	Timing	Established Biomarker	Considerations
Manganese	Whole Blood	Acute	Yes	Limited sensitivity Good marker in occupational studies
	Urine[a]	Unclear	No	Limited validity, urine is a minor elimination pathway
	Hair[b]	Sub-chronic	Yes	Variability with hair color
	Toenail/Fingernail[b]	Sub-chronic	Unclear	Similar to hair manganese
	Teeth	Chronic	Unclear	Correlates well with bone and blood manganese
	Exhaled Breath	Acute	Unclear	Occupational studies only
	Brain	Chronic	Unclear	Requires MRI
Molybdenum	Whole Blood	Unclear	No	Window of exposure relfected is unclear
	Urine[a]	Recent	Yes	Sensitive to changes in dietary intake
	Hair[b]	Unclear	No	Window of exposure relfected is unclear
	Toenail/Fingernail[b]	Unclear	No	Window of exposure relfected is unclear
Selenium	Whole Blood	Acute/Sub-chronic	Yes	Tightly regulated levels
	Red Blood Cells	Sub-chronic	Yes	Tightly regulated levels
	Plasma	Acute	Yes	Decreases with smoking, malnutrition, older age, inflammatory processes
	Selenoprotein P in plasma	Sub-Chronic	Unclear	Heterogeneous findings
	Urine[a]	Recent	Yes	Integrates selenosugars and inorganic selenium
	Hair[b]	Unclear	No	Hair decontamination is very difficult
	Toenail/Fingernail[b]	Chronic	Yes	Good correlation with dietary intake
	Placenta	Unclear	Unclear	Emerging biomarker
Zinc	Whole Blood	Acute		Tightly regulated levels
	Plasma	Acute	Yes	Low sensitivity and specificity, high variability when plasma expansion (e.g., pregnancy) 0.1% of the body burden
	Urine[a]	Acute	Unclear	Sensitive to Zn supplementation but less sensitive to Zn depletion Influenced by conditions that increase protein catabolism such as strenuous exercise and diabetes Changes during pregnancy and lactation
	Hair[b]	Unclear	No	Window of exposure relfected is unclear
	Toenail/Fingernail[b]	Sub-Chronic	Unclear	Subject to seasonal variations

[a] Needs adjustment for urine dilution (creatinine or specific gravity)

[b] Sample requires environmental decontamination