

Metals in the Environment as Risk Factors for Infectious Diseases

Gaps and Opportunities

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Abstract

This chapter aims to provide insights into current knowledge and gaps in our understanding of the influence that trace metals in the environment have on the pathogenesis of infectious diseases. By reducing immune function, trace metal deficiencies may substantially contribute to the global burden of diarrhea, pneumonia, and malaria. Improved methods and biomarkers for assessing the risks of trace metals deficiencies and toxicities are required. Human activities may be contributing to trace metal deficiency in soils and plants, which is a risk factor for infectious diseases in many countries, by exacerbating the preponderance of cereals and cash crops that reduce food diversity and micronutrient intake. Adaptive strategies are needed to reverse these trends. The microbiomes of the body are in the frontline for exposure to metals and crucial in moderating the outcome of host–parasite interactions. Anthropogenic activities have led to increased toxic metal exposure, and effects on human hosts need clarification. Metal toxicities can also impair the immune system and hence increase the susceptibility to infectious pathogens. Climate change affects metal speciation and the build-up of trace elements in the human food chain, with as yet unknown outcomes on infectious disease. Food processing and the use of metallic nanomaterials can alter human exposure to metals in ways that can influence the host–pathogen competition for metals. The effects of metals on human health may also be mediated through modification of the epigenome, conferring drug resistance on pathogenic bacteria and enhancing/reducing human tolerance to infectious parasites. The emerging metals cerium, gadolinium,

lanthanum, and yttrium constitute another driver of change in metal exposure and may potentially modulate the immune system with unknown consequences for human health.

Introduction

Research during the last half century has clearly established that trace metals, whether essential or nonessential, play important roles in a wide variety of processes in living systems and can be a defining factor in the outcome of parasitic infections (Fraga 2005; Winans et al. 2011). From the environmental health perspective, there are currently three anthropogenic drivers of the global biogeochemistry of trace metals that can influence the patterns of infectious diseases by moderating the exposure of human hosts to suboptimal and/or toxic levels of trace metals:

1. The inadvertent contribution of human activities to the epidemic of trace metal deficiency through modern agricultural practices—a problem that affects over one billion people worldwide and is especially prevalent in developing countries.
2. Worldwide contamination of the environment with toxic but nonessential trace metals through industrial emissions, which have overwhelmed the natural cycles of these elements in many ecosystems.
3. Global change, which tends to increase the bioaccumulation of trace metals in the human food chain.

The first trend is related to the venerated Green Revolution, which promoted selective breeding of high-yielding crops that have low concentrations of zinc and other trace metals (Graham et al. 2012). The unintended consequences of the ongoing changes in trace metal balances in natural ecosystems raise concerns as to whether new efforts in developing countries to increase food production and establish emitting factories will further exacerbate the disparities in the global burden of infectious diseases.

The growing worldwide contamination of the environment with toxic trace metals, such as arsenic, cadmium, lead, mercury, platinum, silver, and thallium, and the bioaccumulation and biomagnifications of these heavy metals up the food chain have been well documented (Nriagu 1984). Since these heavy metals have become so widely dispersed, they have the potential to pose a continuous risk for human and animal health globally over a long time period because they are nondegradable. Increasingly, the riskscape used to evaluate this situation (which includes the coexistence of high levels of toxic metal pollution, the high prevalence of trace metal deficiencies, and the high incidence of infectious diseases) is becoming common in many parts of the world. In addition, the potential for interaction of these risk factors is real,

but the consequences for the pathogenesis of infectious diseases have not received much attention.

Burden of Disease Attributable to Metals and Infections

An assessment of “burden of disease” is widely used in public health to evaluate the aggregate impact that risk factors for a disease have on human health. This is usually considered on a disease-specific basis, such as the contribution of salt to the burden of cardiovascular disease or the contribution of cadmium to end-stage renal disease. By implication, this estimate provides a statement of the expected *reduction* in disease burden that can be predicted by reducing or eliminating exposure to the risk factor (e.g., reducing salt intake). Most diseases have multiple effectors and in the case of infectious diseases, which may be caused by a specific pathogen, involve multiple factors (e.g., prevalence, virulence of the pathogen, transmission, host response) that influence the severity of the disease. Separately, trace metal deficiencies or toxicities and infectious diseases contribute substantially to the global burden of morbidity and mortality. Understanding the role of such factors in disease burden is important to national and international public health investments and programs. Thus, it is important to gain a better understanding of the burden of infectious disease that is attributable to deficiencies in essential metals or excesses of toxic metals; that is, the proportion of the load or burden of infectious diseases that is attributable to metal insufficiency compared to that which is attributable to metal toxicity. A unified global effort to mitigate the high burden of disease attributable to insufficiency and toxicity of trace metals, in relation to infectious diseases, should be considered important for achieving the Millennium Development Goals and should drive future research.

The attributable contributions of metal deficiency or toxicity to the global infectious disease burden have been estimated for only a few metals: zinc, iron, lead, and arsenic. From their dietary trials, Black and colleagues (Caulfield and Black 2004; Black et al. 2008) estimate that Zn deficiency in children less than five years old increases the incidence of diarrheal disease by 1.28 (95% CI 1.10–1.50), pneumonia by 1.52 (95% CI 1.20–1.89), and malaria by 1.56 (95% CI 1.29–1.89). From these relative risks, Zn deficiency was estimated to cause 176,000 diarrhea deaths, 406,000 pneumonia deaths, and 207,000 malaria deaths. The loss of worldwide disability-adjusted life years (DALYs) attributable to Zn deficiency was estimated to be 28 million annually and was ranked fifth among the risk factors for mortality and morbidity. Subsequent analysis by Lim et al. (2012) dramatically revised these estimates downward: in 2010, total mortality due to Zn deficiency was estimated to be 97,330. The revised DALY estimate was 9.14 million; this ranked Zn deficiency 31st among the common risk factors contributing to the global burden of disease (Lim et al.

2012). The variation in estimates, however, underscores the lack of knowledge of the moderating influence of Zn deficiency on infectious diseases.

For 2010/2011, reported annual deaths attributable to Fe deficiency worldwide were estimated to be around 105,000 (Lim et al. 2012; WHO 2013a). Estimated DALYs for this risk range from 46–48 million life years (Lim et al. 2012; WHO 2013a). These estimates were based on Fe-deficiency anemia as the primary outcome measure, with the assumption that common infectious diseases (e.g., hemolytic malaria and parasitic and bacterial infections/infestations such as hookworm, trichuriasis, amoebiasis, and schistosomiasis) contribute to deplete stores of iron and hence result in Fe-deficiency anemia. It must be emphasized that the converse is also true: Fe deficiency is present in these diseases and is thus a risk factor with sequelae that can go well beyond the development of anemia. Because of failure to account for all comorbid effects, most estimates of the contribution of Fe deficiency to disease burden may be grossly incorrect or underreported.

In terms of the contribution of heavy metal toxicities to the global infectious disease burden, in 2010, Pb exposure was estimated to have accounted for 674,000 deaths, and the global DALYs attributable to this risk factor are estimated to be 13.9 million life years (Lim et al. 2012). The most recent assessment by the World Health Organization (WHO) did not rank Pb exposure among the top twenty leading causes of global DALYs (WHO 2013a). The contribution of infections to Pb-induced morbidity on the calculated DALYs is unclear.

A number of studies have estimated the DALYs for As exposure in drinking water in Bangladesh (Lokuge et al. 2004; Ahmed et al. 2005). None, however, has considered arsenic as a risk factor for any of the water-related infectious diseases (e.g., cholera, helminth infections, schistosomiasis, and trachoma) that coexist widely with elevated levels of arsenic in local drinking water. The significance of arsenic on risk for infectious diseases remains, therefore, to be established.

Our ability to assess the metal-attributable fraction of the infectious disease burden is severely limited by lack of information on (a) infectious disease endpoints that can be influenced by metal exposures, (b) distribution of exposure to each metal in the population and the effects of coexposure to more than one metal, and (c) etiological effect sizes for the relationships between metal exposure and disease outcome (WHO 2013a). It is hoped that this chapter will draw attention to the need for epidemiological studies to collect these types of information.

A study has been done on small-scale gold miners in watersheds of the Tapajos in Amazonian Brazil who were coexposed to high incidence of infective mosquito bites and elevated levels of methylated mercury (MeHg) from consumption of contaminated fish (Silva et al. 2004; Silbergeld et al. 2005). Increased risks for malaria (diagnosed by thin smear) were found in miners from downstream settlements exposed to MeHg compared to miners in similar

ecosystems that did not use mercury (diamond and emerald miners). High prevalence of endemic malaria exists in many regions of Latin America, Asia, and Africa where intensive artisanal small-scale gold mining is widespread. These settings provide opportunities to conduct epidemiological studies to assess the relationships between metal exposure and malaria.

Animal models of infectious disease have provided insights into the effect of mercury on infectious diseases. Studies have included mercury and malaria in mice (Silbergeld et al. 2005), coxsackievirus B3 (CVB3) and mercury (Nyland et al. 2012), and listeria and both cadmium and lead (Simonet et al. 1984; Kowolenko et al. 1991). These studies have consistently reported that metal preexposures increase the severity of disease in mice. The study of mice infected with CVB3 showed a disturbed Hg balance in the intestine, serum, and brain, as well as infection-induced changes in metallothionein 1 (MT1, a metal-binding/-transporting protein) in the intestine, liver, and brain (e.g., Frisk et al. 2008). This observation was presumed to be a normal response in common infections and the underlying mechanism for the reported findings of Hg changes in blood and tissues. Such results from animal studies (Koller 1975; Beck et al. 1994; Frisk et al. 2007, 2008; Ilbäck et al. 2007) point to serious consequences when infected individuals are concomitantly exposed to potentially toxic metals, such as mercury in their environment.

Coexposures Involving Metals

While metals and their impact on risk for infectious disease are often studied on a one metal and one disease basis, humans are more likely to be exposed to mixtures of metals from their diet and environment. The issue becomes more complex in terms of risk assessment since metals may compete for uptake, distribution, and/or use among the host's immune cells and pathogens. As a result, antagonistic or synergistic effects may operate locally or systemically. Table 17.1 illustrates some examples of reported interactions among and between metals and other frequently encountered environmental factors. This list is not intended to be exhaustive. Among the interactions described in Table 17.1, three patterns are apparent:

1. Metals may act synergistically to cause toxic effects on the immune system. In mice, lead and arsenic caused a greater immunotoxic effect when administered together than when singly administered (Bishayi and Sengupta 2006).
2. In many cases, exposure to toxic heavy metals can result in significant local or systemic deficiencies of nutritionally required metals.
3. Nonmetal factors are also important in coexposure. For example, both dietary fat and dietary protein (source and percentage) can modulate risk of metal-induced host toxicity.

Table 17.1 Select examples of that can affect the host, including immune–microbe interactions.

Metal	Additional Environmental Risk Factor	Outcome
Arsenic	Selenium	Selenium protects against some immunotoxicity (for basal immune profiles) but does not prevent As-mediated oxidative damage
Arsenic trioxide	Genistein	Increased oxidative potential
Cadmium	Lead	Dose-dependent interactions for oxidative-driven neurological outcomes that varies based on developmental window of prenatal coexposures
Cadmium	Lead	Antagonism of the metals for suppression of adult hepatic antioxidant enzyme activities
Cadmium	Selenium	Selenium alters Cd tissue distribution and protects against Cd-promoted innate immune oxidative tissue damage
Copper	Zinc	May synergize to inactivate the exposed Fe-S cluster of key bacterial dehydratase enzymes
Lead	Maternal diet (protein differences)	Partial immune protection
Lead	Arsenic	Increased dose sensitivity of macrophages
Lead	High fat diet	Increased blood Pb levels
Lead	Iron	Fe deficiency increases Pb absorption
Lead	Selenium	In adults, higher Pb levels appear to predispose for Se deficiency
Selenium	Vitamin E	Some sparing against oxidative damage
Iron	Aluminum	Reduced Fe levels in lymphoid tissues
Iron	Gallium	Reduced Fe availability
Iron	Cobalt	Reduced Fe availability
Iron	Copper	Copper influences Fe recycling in macrophages
Manganese	Zinc	Interaction in innate immune, calprotectin-mediated host defense
Vanadium	Magnesium	Magnesium protects against Vd-associated, oxidative-induced anemia
Zinc	Excessive alcohol	Zn deficiency for macrophages
Zinc	Lead	Replaces zinc in critical enzymes
Zinc	Cadmium	Replaces zinc in critical enzymes

Potential for Leveraging Information from Current Population Studies

Considerably more information is required to establish with certainty the role that heavy metals (deficiencies or excess) play in the pathogenesis, morbidity, and mortality of infectious diseases globally. However, some existing and on-going studies can be used to obtain data on associations between deficiency of metals and infectious diseases. These include the National Health and Nutrition Examination Survey (NHANES) in the United States, the National Children's Studies (NCS) in many countries and regions, and the EU ZINCAGE study. In a recent cross-sectional study, Xu et al. (2013) used NHANES 2003–2010 to compare exposures to heavy metals (including cadmium, lead, and total mercury) in HIV-infected and non-HIV-infected subjects in the United States. They found that HIV-infected individuals had higher concentrations of all heavy metals than the non-HIV infected group. HIV status was significantly associated with increased blood cadmium ($p = 0.03$) after adjusting for age, sex, race, education, poverty income ratio, and smoking. However, HIV status was not statistically associated with lead or mercury levels after adjusting for the same covariates. Xu et al. concluded that exposure to cadmium was a contributing factor to the higher prevalence of chronic diseases (e.g., cardiovascular diseases) among HIV-infected subjects.

A study based on the Korea National Health and Nutrition Examination Survey (KNHANES) from 2009–2010 explored the additive effects of metals on metabolic syndrome, a constellation of cardiovascular risk factors, including central obesity, hypertension, dyslipidemia, and impaired glucose tolerance (Moon 2013). Although the effect of individual heavy metals (specifically lead, mercury, and cadmium) on metabolic syndrome was weak, the combined heavy metal exposure affected metabolic syndrome more synergistically than individual exposure in the general Korean population. Together, the NHANES and KNHANES studies suggest that metals and infections give rise to similar comorbidities in the form of metabolic syndrome.

Currently, the NCS in the United States is examining the effects of the environment—broadly defined to include factors such as air, water, diet, noise, family dynamics, community and cultural influences—and genetics on the growth, development, and health of children across the United States. The NCS study follows children from before birth until 21 years of age. The goal of the study is to improve the health and well-being of children and to expand understanding of the role that various factors have on health and disease. There should be enough information in the resulting data base to permit the assessment of possible comorbidities attributable to coexposure to trace metals and pathogenic organisms. Another large study that is currently underway is the Japan National Study on Children and the Environment, which has already enrolled over 100,000 infants. It is similar in design to the NCS in terms of methods, data collection, and biosampling in a longitudinal design and can be used similarly to assess comorbidities from metal–pathogen interactions.

Metal Sufficiency, Deficiency, and Toxicity within the Context of Infections

The lack of clarity in the definitions of deficiency, susceptibility, and toxicity of metals in relation to infectious disease leads to difficulties in determining these parameters. Here we wish to highlight the main issues involved. For further discussion, see Rehder et al. (this volume).

Conflicts in Principles and Methods Used to Determine Sufficiency and Deficiency of Essential Trace Elements

Different principles and methods have been used by various governmental agencies to establish (a) recommendations designed to protect the public from the toxic effects of trace metals (including essential ones) and (b) advisable safe intakes aimed at protecting the public from the adverse effects of deficiency. This has often resulted in conflicting recommendations. To highlight one example, consider the recommended dietary allowances (RDAs)—established by the U.S. Food and Drug Administration (FDA) and the U.S. National Research Council to ensure adequate nutritional intake of trace metals to maintain normal physiological functions—and the reference dose (RfD) or daily exposure levels—set by the U.S. Environmental Protection Agency to protect the public from trace metal toxicity: Because of uncertainties inherent in toxicity evaluation, RfDs must often include uncertainty factors to provide sufficient margin of safety (especially for vulnerable groups). This, in turn, can bias the RfD estimate toward the low side. For mercury in fish, the current RDA is substantially higher than the RfD; this has led to conflicting fish consumption advisories in the United States and created public confusion. Such conflicts point to the need for new principles and methods in the assessment of risks of essential trace metals: nutritional and toxicological information must be considered in a balanced way (WHO 2002). Such a unified approach should provide a coherent framework for assessing the moderating effects of trace metals on infectious diseases.

Biomarkers to Establish Links between Metal Exposure and Infectious Disease

Biomarkers, defined as an indicator of some biological state or condition, reflect changes in the organism's metabolism in response to an exposure (or lack thereof). Biomarkers have greatly expanded the scope of epidemiological and toxicological research by providing insights into events that couple exposures and diseases or dysfunctions. In addition, they inform knowledge of events within the organism that connect changes in exposure with changes in health. This approach allows us to test hypotheses as to the processes of pathophysiological response and generates useful information on early signals

of adverse effects associated with exposures. Figure 17.1 illustrates the metal pathways that link metal exposure to infectious disease. To the standard model (Silbergeld and Davis 1994), we have added the microbiome at the interface between the external exposure and the internal dose to denote the importance of microbial events in absorption. Each point on the diagram represents a potential biomarker.

The concept of body metal status (i.e., whether the body contains amounts of metals that are sufficient for optimal biological processes) is not well defined, yet it is central to the development of RDAs (Aggett 1991). In assessing metal status, the question of whether subjects are deficient, at risk of being deficient, have adequate body levels, or are experiencing metal toxicity cannot often be answered simply, particularly if the metal (such as zinc) has numerous biological functions. A common host response during acute bacterial, viral, and parasitic infections is an increase in the synthesis of metal-binding proteins in several target organs involved in the infectious process (Beisel 1998; Ilbäck et al. 2004). This may result in significant changes in the dynamics and concentrations of both essential and nonessential trace elements in blood and tissues that are used as biomarkers (Beisel 1998; Ilbäck et al. 2003). A significant amount of work has been done on disease-related redistribution of the essential trace elements following an infection, and a number of proteins that can serve as metal carriers have been identified: Fe-binding ferritin, divalent metal transporter 1 (DMT1), Cu-binding ceruloplasmin, and Zn-binding MT1–MT4 (Beisel 1998; Nordberg and Nordberg 2000; Ilbäck et al. 2004). Since trace elements are required for host defense processes, a flux of trace elements between blood and other tissues, including the tissues that are involved in the disease, is usually orchestrated during active infection (Beisel 1998; Frisk et al. 2007). Although less is known about infection-induced changes in nonessential trace elements, changes have been described that may not be favorable to the host:

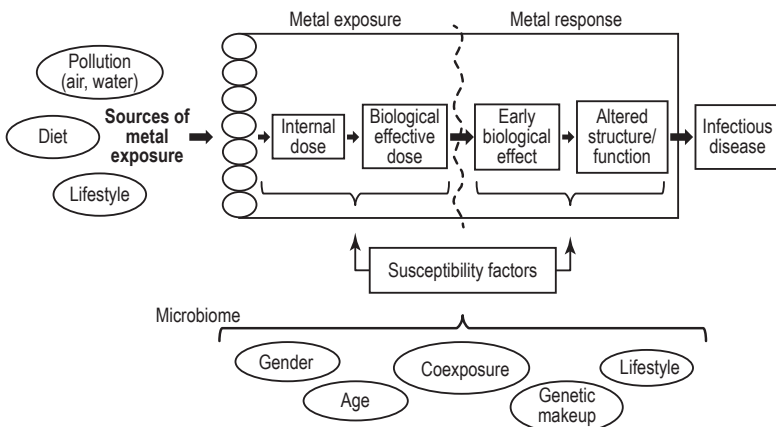


Figure 17.1 Metal pathways that link metal exposure to infectious disease.

an increased redistribution of cadmium from the liver to the kidneys (Ilbäck et al. 2004), increased Hg concentration in red blood cells (Frisk et al. 2007), or increased loading of arsenic, cadmium, copper, and zinc into the brain (Ilbäck et al. 2007). Biomarkers provide important information about metal status in different tissues and organs with respect to deficiency or toxicity, and they assist in establishing the impact of metal deficiency on infectious disease.

Global Trends in Trace Metal Deficiency with the Potential to Impact on Infectious Diseases

Trace metal deficiency in soils and plants is a risk factor for infectious diseases in many parts of the world. From 190 major agricultural soils, it is estimated that 49% are deficient in zinc, 31% deficient in boron, 15% deficient in molybdenum, 14% deficient in copper, 10% deficient in manganese, and 3% deficient in iron (Sillanpää 1982; Graham et al. 2012). In general, soils associated with trace metal deficiencies include neutral and calcareous soils, intensively cropped soils, paddy soils and poorly drained soils, sodic and saline soils, peat soils, soils with high available phosphorus and silicon, sandy soils, as well as highly weathered acid and coarse-textured soils; these types of soils are widespread in many parts of the world (Singh 2008; Lyons and Cakmak 2012). Low availability of zinc and other trace metals in such soils is one of the most widely distributed stressors in world agriculture, especially in southeast Asian countries and Australia (Brennan and Bolland 2006; Singh 2008; Lyons and Cakmak 2012). More than 85% of the cereal-growing areas in India are affected by low zinc (Singh 2008). Cereals and wheat grown in such soils are liable to be deficient in zinc and other trace metals, leading to low crop yields and decreased nutritional quality of the food (Bouis 2003; Cakmak et al. 2010).

The preponderance of cereals and cash crops in modern cropping systems and worldwide adoption of high-yielding cultivars have combined to reduce our food diversity and micronutrient intake in ways that can impact the immune system (Govindaraj et al. 2011; Graham et al. 2012). Today, production of various wild, traditional, or ancient food crops, which are genetically very diverse and may be rich in trace elements, has been largely displaced by crops of the modern agricultural system (Welch and Graham 2005; Birner et al. 2007; Graham et al. 2012). The latter has contributed to a decrease in cereal prices and an increase in price for legumes, fruits, vegetables, and animal and fish protein; this has led to the so-called “hidden hunger” or micronutrient deficiency brought about by these less nutritious cereal crops becoming more affordable and available (Cakmak et al. 2010). Among widely cultivated food crops with high-yield capacity, wheat plays a particularly important role in daily energy intake (especially in the developing countries), accounting for about 50% of daily energy intake in many Central Asian and Middle Eastern countries (Lyons and Cakmak 2012). Such high-yield wheat cultivars are poor sources of micronutrients, especially zinc and iron, and are rich in anti-nutritional

compounds such as phytic acid and phenolic compounds, which reduce biological availability of zinc and iron in the human digestive tract (Graham et al. 2012). The factors which lead to a reduced availability of trace elements in crops occur in areas of the world with high incidence of infectious diseases.

Food Systems Approach to a “Greener Revolution”

Until recently, micronutrient deficiency was primarily viewed as a soil or (to a lesser extent) plant problem. More importantly, though, it needs to be addressed as a human health problem—one that impacts susceptibility to infectious diseases.

The unintended consequences of the Green Revolution, which promoted micronutrient deficiencies in the human population (reviewed by Bouis et al. 2012; Graham et al. 2012), has prompted a growing call for agricultural technologies that can sustainably meet the increasing food demands of the world’s expanding population while providing adequate supplies of bioavailable trace elements and micronutrients for public health. Conceptual models have been advanced for such food systems, including a farm-to-fork approach that is focused on cropping systems and their abilities to support balanced human nutrition in sustainable ways (Welch et al. 1997; Lyons and Cakmak 2012). This approach aims to increase diversity (re-diversification) of cropping systems, particularly with respect to indigenous fruits, vegetables, and pulses, and developing trace metal dense cultivars of staple crops. In addition, it advocates finding a more effective means of using the iron and zinc contained in cereal brans (which are often removed during food preparation) and developing appropriate technologies to preserve and store foods (Coombs 2000; Welch and Graham 2012; Thompson and Amoroso 2013). Such new strategies need to address simultaneously the demand of the growing human population for food and a balanced nutrient output, in the context of environmental, economic, and social sustainability. Such a “greener revolution” differs from the traditional concept of agriculture, which measures its success in terms of crop production (bushels per acre yields) or cost in dollars per year; indeed, the new system would expand that view to include measures of impact on human nutrition and health. To provide improved trace element nutrition and potentially lessen the risk for infectious diseases, a greener revolution must include adaptive strategies to reverse micronutrient deficiencies.

Metal Pathways and Metals in the Microbiome

“Exposure” to metals occurs outside the organism through, for example, air and water pollution, diet, or lifestyle (cigarette smoking is a major source of exposure to lead and cadmium). The metals in an exposure pathway (Figure 17.1), such as air, water, and food, are then presented to the organism primarily

through inhalation, ingestion, or dermal contact. Processes of absorption mediate transfer of metal-containing substances into the internal environments of the organism. As illustrated in Figure 17.1, the microbiome (vertically stacked circles) is situated at portals of entry, such as the gut and skin, at the boundary of the organism.

The Importance of the Microbiome

The microbiome is a microbial community within a specified niche (e.g., within an organ system or ecologic space) or a community of all microbes, chemicals, and inputs/outputs related to the microbial system. This field of study received a great boost in 2007, when the National Institutes of Health initiated the Human Microbiome Project with the intent of surveying and characterizing the microbes that reside at different body sites (Turnbaugh et al. 2007). The seminal report on microbes from 18 body sites in over 240 healthy volunteers revealed the complex nature of the human microbial inhabitants and the incredible amount of both intra- and interpersonal variation in the communities that inhabit the human body. Nonetheless, how the availability of critical trace elements influences the biotic composition and distribution at each site has yet to receive any attention.

Some microbiomes (e.g., the skin, gastrointestinal tract, and lung) reside at the portals of host exposure to the environment. In the schematic model of biomarkers of exposure and outcomes (Figure 17.1), these microbiomes may represent a front line for exposure to metals, whether via inhalation, ingestion, or dermal route. It is the place where the human host first encounters microbiota and environmental sources of metals. In the following, we introduce a modified exposure–outcome biomarker model to include the microbiome as a significant early stage component affecting host exposure and immune-related host defense. A potentially critical target of heavy metal exposures during development is disruption of complete attainment of the normal adult human microbiome. The processes involved may include interactions that take place in the microbiome (gut but possibly others such as oral and lung), in terms of metabolizing the trace metals as well as removing toxic heavy metals from the organism prior to absorption through the epithelial layer.

Gut Microbiome

The gut has the largest microbial community in the human body and contains at least two orders of magnitude more genes than are found in the human genome (Reid 2010). Microorganisms in the human gut microbiome have developed coping strategies to transform a toxic metal into a less harmful form or to bind the metal intra- or extracellularly, so as to prevent harmful interactions within the host cell (Diamond et al. 1998; Monachese et al. 2012).

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The gut microbiota can influence two processes pertaining to metals: (a) detoxification in relation to the removal of drugs, mutagens, and other harmful agents from the body, and (b) detoxification to prevent the entry of damaging compounds into the body (Berhane et al. 1994). Detoxification occurs in the human intestinal tract, liver, and kidneys where microbes reduce or moderate the forms and concentrations of toxic metals (Ibrahim et al. 2006). Gut microbiota may also have a major role in binding metals, preventing their entry to the body and thus protecting the host. The extent of detoxification depends on the route of entry, the foodstuff consumed, and the types of host microbiota (Sun et al. 2012). The effects of gut microbiota on the sequestration and detoxification of toxic metals and the extent that these microbes provide protection to the human host remain an area for systematic investigation. One recent study has shown that perturbations in the gut microbiome composition of mice can lead to gut microbiome phenotypes that significantly affect As metabolic reactions, including reduction, methylation, and thiolation (Lu et al. 2013). While some of the observed associations between changes in trace metals, microbiota composition, and disease condition may be no more than epiphenomenal, the critical role of safe and essential levels of trace metals in maintaining a healthy gut ecology must nevertheless be recognized.

An interesting idea of employing certain members of the gut microbiota to reduce metal toxicity in humans was recently proposed (Monachese et al. 2012; Marco and Tachon 2013). Lactobacilli and possibly other bacterial types used in the food industry or as probiotics have the ability to bind and sequester metals and prevent their entry into human organs (Ibrahim et al. 2006). Such “bioremediation” of the human body using microbiota-modifying approaches has several advantages:

- They do not require expensive technology or infrastructure.
- They can be based on locally produced foods, such as yogurt made in the home or community.
- Local acceptance is assured.

This intervention strategy potentially represents an affordable option for billions of people around the world who are being chronically exposed to toxic metals in their environment (Reid 2010). The potential for the human microbiome to be modulated has applications to some clinical conditions, such as ulcerative colitis (Torres et al. 2013), and may be applicable to other diseases including infectious diseases.

Oral Microbiome

The human oral cavity is heavily colonized by microorganisms, including viruses, protozoa, fungi, archaea, and bacteria. Unlike the commensal microbiota found at other body sites, which seemingly live in harmony with the host, the normal microbiota of the mouth is responsible for the two most common

diseases of humans: dental caries and periodontal diseases (Wade 2013). It has long been recognized that caries is an infectious and transmissible disease that can be moderated by trace metal deficiency or excess in the oral cavity. No specific microorganisms or properties of microorganisms are solely responsible for the initiation and progression of caries. Of the key bacteria in saliva samples, mutans streptococci are probably the most cariogenic microorganisms because of two special features: (a) their high acidogenic and aciduric capacity and (b) their ability to produce extracellular polysaccharides, resulting in the adhesion of dental plaque on tooth surfaces (Larmas 1993). Both processes can be affected by trace metals. Another important group of bacteria is the salivary lactobacilli, which indicate the presence of a caries-type oral environment and are predictors of the progression potential of the lesions (Larmas 1993). Trace metal deficiency and excess have been found to inhibit the growth of these and other plaque species (He et al. 2002). The strongest evidence for stimulatory effects of trace metals on caries prevention comes from the anticalculus and anticaries effects, antibacterial activity, and antiplaque efficacy of many trace metals which have been repeatedly shown in human and animal studies (Lynch 2011). Although a number of human studies have reported significant positive associations between trace metal levels in teeth and saliva and dental caries (Blanusa et al. 1990; Burguera et al. 2002), there are still open questions regarding the mechanisms of pro-caries action and the effects of trace metals on the microorganisms in terms of caries promotion.

Trace metals can influence the differentiation of oral mucosa (Meyer et al. 1981) and the aggregation and adhesion characteristics of dental caries-associated microorganisms (Boosz et al. 1983). The oral microbiome is a unique system for understanding the role of trace metals on its ecology and how the microbiome affects the fate and effects of the metals. There is clearly a need for methodologies that can be used to test the cariogenic properties of the trace metals and how the forms of metals in saliva relate to the diversity and composition of cariogenic bacteria in the oral cavity.

Influence of Genetic Factors

Some of the more common polymorphisms (> 5%) involve genes that also play a role in the immune response to infections (e.g., interleukin 6). There are also genes known to regulate toxicokinetics and toxicity of toxic metals, such as arsenic, mercury, and lead. The natural resistance-associated macrophage proteins (Nramp1 and 2) are proton-dependent solute carriers of divalent metals such as Fe^{2+} and Mn^{2+} (Slc11a1 and 2). Their expression in both resting and microbicidal macrophages, which metabolize iron differently, raises questions about the Nramp mechanism of Me^{2+} transport and its impact in distinct phenotypic contexts (Cellier 2012). NRAMP1, vitamin-D receptor, and tumor necrosis factor α (TNF- α) gene polymorphisms have been associated with susceptibility to infectious diseases, but the results have been inconsistent (Merza

et al. 2009). In addition to NRAMP, polymorphisms in other metal-related genes have been associated with toxicity effects of metals. For lead, the most significant (and prevalent) gene is that encoding the enzyme δ -aminolevulinic dehydrase (ALAD). The ALAD protein is a significant binding site for lead within the erythrocyte and thus regulates erythrocyte:plasma toxicokinetics for lead. A common polymorphism in the ALAD gene (G177C) can alter plasma Pb concentrations significantly, by 1.66-fold (Montenegro et al. 2006). Another example is the gene that expresses metallothionein. Metallothioneins are a family of intracellular proteins that bind metals and may provide protection against metal toxicity (e.g., zinc, copper, and cadmium). A study in Chinese populations found that a mutation in the gene that encodes MT1A (a Cd-binding form of the protein) was associated with significant increases in blood cadmium and urinary β -2 microglobulin, which is a biomarker of renal toxicity (Lei et al. 2012).

Gender, Metals, and Infections

Gender (as distinct from genetics) is also associated with essential metal status, toxic metal levels, and infectious disease. In some cases this involves gender-specific differences in diet and behavior. Infectious disease incidence is often male biased. Two main hypotheses have been proposed to explain this observation. The physiological hypothesis emphasizes differences in sex hormones and genetic architecture, whereas the behavioral hypothesis stresses gender-related differences in exposure. The population-level predictions of these hypotheses have yet to be thoroughly tested in humans. After puberty, disease incidence is male biased in cutaneous and visceral leishmaniasis, schistosomiasis, pulmonary tuberculosis, leptospirosis, meningococcal meningitis, and hepatitis A. Severe dengue is female-biased, and no clear pattern is evident for typhoid fever. For most diseases, male bias emerges during infancy, when behavior is unbiased but sex steroid levels transiently rise. Behavioral factors likely modulate male-female differences in some diseases (e.g., the leishmaniasis, tuberculosis, leptospirosis, or schistosomiasis) and age classes. The immune system is known to be biased by gender, with genetics, hormonal status, and other factors contributing to male-female differences. As a result there are differences between men and women in terms of infection and severity of many infectious diseases as well as postinfection sequelae (McClelland and Smith 2011).

To date, few studies have examined sex differences in immune response to metals. Silva et al. (2005) report on the effects of prenatal exposures of BALB/c mice to HgCl on the ontogeny of the immune system. Immune function was assessed by collection of cells from lymph nodes, spleens, and thymus from postnatal day 11 through 60 and studied in male and female mice. Organ-specific effects were observed on maturation. At maturity, females and males differed in terms of effects: in females there was an overall decrease in

ConA-stimulated cytokine release from cells *ex vivo*, whereas in males, there was an overall increase in release (both compared to unexposed mice of the same strain and gender). Similar gender-specific effects after *in utero* exposure to HgCl were reported by Pilonis et al. (2009).

Growing evidence indicates gender differences in susceptibility to disease infection and in response to metal exposure. However, limited attempts have been made to examine the relationships between these two factors in the pathogenesis of infectious diseases among males versus females. More studies are required to understand the basis of the differences in metal metabolism between males and females.

Impacts of Metals in the Environment on Infectious Diseases

Mining, smelting, and widespread use of metals to support the expansion of human industrial activities have led to an exponential increase in the amounts of heavy metals that are released into the atmosphere, water, and soil. Anthropogenic inputs have overwhelmed the natural biogeochemical cycles of many elements in many ecosystems (Nriagu 1984). As a consequence, all life forms on Earth are being exposed to a wide range of toxic metals in the environment, which they might not have encountered previously in their evolutionary cycle. As a matter of necessity, many organisms have evolved unique mechanisms which allow them to survive and, in some instances, reduce the toxicity of metals in their environments. The extent to which such coping strategies can be used by pathogens to moderate the influence of new metal compounds on their interactions with human host is a matter that has received little study.

Sources and Emissions of Toxic Metals

Most of the available information on sources and emissions of toxic metals relates to mercury, lead, cadmium, and arsenic, which are emitted from both anthropogenic and natural sources. For these metals, information is available on geochemical cycling and pathways in the environment as well as on uptake into biota, including the food chain. The most recent and accurate information available is for mercury. The major anthropogenic sources of Hg emissions at present and expected in the future derive from coal combustion, followed by release of mercury as a result of artisanal gold mining and production (Pacyna et al. 2010; UNEP 2013). As much as 2000 metric tons of mercury are emitted annually from anthropogenic sources, and similar amounts are being released from natural sources, including the reemissions of mercury from land and water surfaces (Pacyna et al. 2010). Nonferrous metal smelting and other industrial processes are the main emission sources for the remainder of the abovementioned metals.

An important group of metals in the environmental context consists of other well-known metals, such as vanadium, nickel, copper, zinc, chromium, silver, antimony, gold, thallium, rare earth elements (REEs), and the platinum group of metals (PGMs). Major emission sources, applications, and exposure pathways of all of the abovementioned metals are presented in Appendix 17.1, which also includes information on the possible impact of metals on the immune system as well as their antiviral and antimicrobial properties. As listed in Appendix 17.1, proximate sources of human exposure to toxic metals are not limited to direct consumption of contaminated food but can include inhalation of contaminated air and other specific practices (e.g., tobacco smoking) as a major source of exposure to lead and cadmium. Even though most countries have removed Pb additives from automotive fuels, crude oil still contains substantial amounts of naturally occurring lead. As a result, some unleaded gasoline may contain up to 15 mg/l of this element. It should be noted that emissions of many metals, particularly mercury, occur at local and regional scales, especially in the developing countries with high rates of endemic diseases, such as malaria, leishmaniasis, and dengue.

Metal Emissions and Lung Infection

Particulate matter exposures are associated with increased risks for human infections, and this association is so rampant that, historically, particle-related disease was frequently, but erroneously, regarded as a variety of infection (e.g., coal workers' pneumoconiosis was previously referred to as "miners' consumption" and "miners' phthisis") (Ghio 2014). Once inhaled, particles are deposited in the nose, pharynx, larynx, trachea, bronchi, and distal lung. It is not by coincidence that the respiratory tract is the system most frequently infected after particulate exposure. Exposures to particles from mining and smelting, fossil fuel combustion, biomass burning, metallurgical works, transportation-related emissions, agricultural work, cigarette smoking, work, environmental tobacco smoke (ETS), wood stoves and gas stoves, as well as ambient air pollution have all been associated with an increased risk for respiratory infections (Ghio 2014). For instance, particulates from cigarette smoking, biomass burning, mining, smelting, and ETS have been linked to an elevated risk for tuberculosis, atypical mycobacterial infections, and meningitis. One possible explanation for particle-related infections is that the surfaces of airborne particulates, especially from anthropogenic sources, are enriched in essential trace elements. Particles deposited in the respiratory tract thus represent a reservoir of essential trace elements which the infective pathogens can exploit to meet their metabolic needs. In addition, particulate surfaces contain nonessential metals (mercury, cadmium, arsenic, beryllium, and manganese) which can increase the risk for infection through moderating the immune response. As an example, elevated levels of serum lead and mercury and low levels of zinc and selenium have been associated with recurrent wheezing in children (Razia

et al. 2011). Children with recurrent wheezing are much more susceptible to respiratory tract infections than healthy children, and trace metals could significantly influence the pathogenesis of the recurrent wheezing.

Changes in energy sources (so-called energy mix), manufacturing, and new technologies are changing the physical and chemical characteristics of the aerosols emitted, and hence their effects on human respiratory health (Pacyna and Pacyna 2001). In addition, we are experiencing a geographic shift in terms of where metals are emitted most intensively: from North America and Europe to Asia. These changes have resulted in significant risk overlap in the developing countries and have involved a juxtaposition of metal hazards from modern industries and the so-called traditional hazards typically associated with infectious diseases. Such risk overlap can contribute both directly and indirectly to global health disparities.

Global Drivers of Change in Metal Exposure

Climate Change

The twentieth century has witnessed an era of unprecedented, large-scale anthropogenic changes to the natural environment which have influenced the emergence and spread of infectious diseases. Recent studies (Jia et al. 2010; Li et al. 2012; Stern et al. 2012) have shown that climate change is already having a significant impact on many aspects of the transport pathways, speciation, and cycling of trace elements in many ecosystems. How the overwhelming modification of the natural cycles of the trace elements by human activities feeds into this global change/infectious disease link has not received much attention. In this regard, the effects of changes in trace metal levels (to deficiency or subtoxic levels) on the establishment and spread of indirectly transmitted, vector-borne anthroponoses (e.g., malaria, dengue fever, yellow fever) has to be of special interest. We need to understand to what extent the trace metal nutriture in changing ecosystems can influence the vector–pathogen link in the transmission chain. In this sense, it would be good to know how the nonhuman life cycle of the pathogens would respond to changes in trace metal exposures that are driven by climate change.

More generally, climatic change and heavy metal stress can influence various processes in plants, including growth, physiology, biochemistry, and yield, and can hence pose a threat to food security (see review by Rajkumar et al. 2013). Elevated atmospheric CO₂ levels have been shown to enhance biomass production and metal accumulation in plants and have been linked to the ability of plants to support greater microbial populations and/or protect the microorganisms against the impacts of heavy metals (Li et al. 2010b; Guo et al. 2011; Kim and Kang 2011). Climatic change can influence metal bioavailability in soils and consequently affect plant growth by moderating the function and structure of plant roots and diversity and activity of rhizosphere

microbes (Sardans et al. 2008; Rajkumar et al. 2010). Better understanding of how plant–metal interactions respond to climatic change is essential in developing high-yielding crops that can tolerate multistress conditions without accentuating the toxic metal levels and compromising future food security.

Food Processing

Another issue that affects human intake of both essential and toxic metals is food processing. Cooking can be a source of exposure to toxic metals (e.g., from the cooking water) as well as a cause of depletion of essential metals from food. Certain ceramic cookware, for example, has been associated with Pb exposure, and some cooking methods may deplete the essential metals in foods (Villalobos et al. 2009). Processing of grains including wheat, rice, and sugar substantially lowers their trace element concentrations. The process of milling rice and wheat removes the bran which contains the major portion of zinc (Borresen and Ryan 2014). Loss of trace elements in refining of wheat to produce white flour results in a 78% loss of zinc, 16% loss in selenium, 86% loss of manganese, and 68% loss of copper; white sugar contains 40 times less zinc than raw sugar, and nearly 6 times less copper (Schroeder 1971). Removal of the essential trace metals during food processing is likely to reduce the immune-boosting capacity of the diet and increase the consumer’s susceptibility to infectious diseases.

Metals in Infant Nutrition

An infant’s gut is particularly sensitive to colonization patterns as inherent intestinal defense mechanisms are immature, and immature intestinal epithelial cells are known to have exaggerated inflammatory responses to both commensal and pathogenic bacteria (Mshvildadze and Neu 2010). Since the core microbiota formation is dependent on exposure to the microbes that first colonize the gastrointestinal tract (“founder species”), the establishment of a “healthy” microbiota in the first days of life after birth is expected to be critical for normal development. It is expected that the trace metals status would be one of the important moderating factors that may reduce the normal commensal microbiota colonization and impair beneficial stimulation of gastrointestinal mucosal development as well as innate and adaptive immune responses. During the first one to two years of life, the microbiome of a healthy human infant evolves toward a typical adult microbiota (Palmer et al. 2007; Dave et al. 2012). Infants, in particular neonates, are reported to be at a higher risk from insufficiency of essential metals or from exposure to toxic levels of metals. The role of trace metals on the dysbiosis and metabolic programming during this highly vulnerable period in the development of their gut microbiome should be presumed to be important, but is unknown at this time.

Recent studies have shown that human milk, instead of being sterile, presents a continuous supply of commensal, mutualistic, and/or potentially probiotic bacteria to the gut microbiome of an infant. These bacteria can contribute to the reduction of the incidence and severity of infections and maturation of the immune system in the breastfed infant, among other functions. The introduction of early formula feeding, either exclusively or in combination with continued breast-feeding, reduces or negates the protective benefits of breast-feeding, as is occurring in countries where mixed feeding practices in infants less than six months have become commonplace. The WHO has reported that only one-third of infants worldwide were exclusively breast-fed during the first six months of life in 2009, the majority receiving some other food or fluid in the early months (WHO 2009). In terms of essential metals, levels in infant formulas have been reported to be from 3–100 times higher than the concentrations found in breast milk, depending on the particular metal. For example, three times higher levels of zinc have been found in infant formulas (based on cow milk) than breast milk and 100 times higher levels of manganese in infant formulas (based on soy milk) (Aschner and Aschner 2005). The high concentrations, due to the fortification of formulas with these essential metals, have been justified in the past because of differences in their bioavailability in infant formulas compared to breast milk. However, currently there is less clarity, and the levels of fortification need to be reassessed in light of the low intake of these elements in the breast-fed infant and the possible deleterious consequences of metal overload which could influence host infections (Ljung et al. 2011; Bornhorst et al. 2013). The high intake of zinc with infant formula may account for the difference in the gut microflora of breast- and formula-fed infants, and the differing microbiome phylotypes may account for the increased susceptibility of formula-fed infants to infectious agents.

Metals in Fast Foods

The gut microbiota of people in the Western World is significantly different (reduced in diversity) from that of people who live in rural villages in developing countries and are habituated to traditional lifestyles (Bengmark 2013). This difference is usually attributed to the fact that the great majority of ingredients in the industrially produced foods consumed in the West are absorbed in the upper part of the small intestine, and thus of limited benefit to the small intestinal and large bowel microbiotas. Lack of proper nutrition, including safe and essential levels of trace metals for gut microbiota, has been implicated in dysfunction of gut ecology, dysbiosis, chronically elevated inflammation, and the production and leakage of endotoxins through the various tissue barriers and hyperactivation of the immune system (Mshvildadze and Neu 2010; Quigley 2013). In addition, heat- and storage-related treatments can result in the formation of the so-called advanced glycation end products and advanced lipoxidation end products in such foods as dairy products (especially powdered milk, which is

frequently used in industrially produced foods), deep-fried foods, grilled meat and poultry, smoked and cured foods, as well as coffee. Consumption of such foods, which are often the main constituents of fast foods, has been linked to inflammation and immune system modulation (Bengmark 2013).

Fast foods have been reported to provide concentrated calories but decreased levels of micronutrients (Bowman and Vinyard 2004; Wimalawansa 2013). Regular consumption of such foods can induce a dysbiosis in the gut bacteria that synthesizes and converts a variety of compounds to impact the physiology, immunity, and presumably the susceptibility or resistance of human individuals to infection. Exposure to elevated levels of nonessential metals and/or suboptimal amounts of essential trace metals due to consumption of fast foods clearly has the potential to impact the gut microbiota and susceptibility to infections in profound ways. Thus more research needs to be focused on this topic.

Epigenetic Effects of Metals

Epigenetics is a term that encompasses events in the genome which affect gene expression without direct changes in gene structure, such as deletion or mutation. These events can be heritable. During the early stages of pre- and postimplantation development of the zygote, programmed silencing and/or activation of specific events is key to normal ontogeny (Christensen and Marsit 2011). DNA methylation is the most widely studied epigenetic marker. Epigenetic changes, which may be stable mechanisms or have some plasticity, are likely to emanate from the environment; thus it is important to characterize the role of environmental exposures in epigenetic alterations. Existing evidence that implicates the role of environmental factors on epigenetic changes comes from studies of diseases such as cancer and adverse reproductive/developmental events. A contribution of heavy metal emissions to human health may be mediated through epigenetic effects that affect susceptibility or response to infection. The flexibility of epigenetic responses is a critical mechanism of both innate and adaptive immune responses in which gene expression is rapidly altered to respond to the presence of an antigen or other stressor, as well as accomplishing the achievement of the mature immune response repertoire (Kondilis-Mangum and Wade 2013).

Evidence of the epigenetic effects of metals on infection is illustrated by data which shows that Zn deficiency *in vitro* increases interleukin (IL)-1 β and TNF- α mRNA and protein, which is associated with increased accessibilities of IL-1 β and TNF- α promoters in Zn-deficient cells (Wessels et al. 2013). The cellular basis of the chromatin-remodeling process induced by Zn deficiency is, however, not clear.

Arsenic is the most frequently studied metal, in terms of its effects on the methyl donor pool, as it is progressively metabolized to a mono- and a dimethyl species (see review by Reichard and Puga 2010). Early life exposure to

arsenic has been linked to altered immune function in children in Bangladesh, where children exposed to arsenic via contaminated groundwater have an increased incidence of respiratory infections and reduced thymic function (Winans et al. 2011).

Other metals for which epigenetic effects have been reported include nickel, cadmium, and chromium VI (Salnikow and Zhitkovich 2008; Arita and Costa 2009). Exposure to diesel exhaust particles, often enriched in heavy metals, is associated with an increase in global hypomethylation and hypermethylation of the promoter of several genes, including *IFN- γ* and *FOXP3* (Liu et al. 2008; Brunst et al. 2013). Diesel exhaust particles were shown to induce *COX-2* expression through histone modification of H4 near the *COX-2* gene promoter (Cao et al. 2007). As *IFN- γ* and *FOXP3* are involved in the immune response and *COX-1* is proinflammatory, exposure of bronchial epithelium to metal-containing particulate matter may have an impact on susceptibility to respiratory infection (see above). It is likely that other metals may have significant epigenetic effects.

Available information shows that pathogens and heavy metals can activate or suppress gene expression through epigenetic modifications, and these changes can last throughout life (Ho et al. 2012). The epigenetic targets of some heavy metals are often similar to those of pathogens and include changes in (a) DNA methylation patterns, either at the global or the individual gene level; (b) the histone code, affecting histone methylation, acetylation, ubiquitination, and phosphorylation; and (c) miRNA expression (see review by Ho et al. 2012). Whether these epigenetic changes are enhanced or suppressed during coexposure to metals and infective pathogens is unknown at the present time.

Metalliferous Nanoparticles and Infections

Nanotechnology has been applied in the food sector and is used for various purposes such as food supplements, functional food ingredients, and food packaging (Sonkaria et al. 2012; Chen et al. 2014). Opportunities to exploit and develop nanomaterials have resulted in a large number of patents worldwide. Nanomaterials can be found in the form of uncomplexed metals, inorganic metals, and carbon-based compounds. Inorganic nanoparticles of silver, titanium, aluminium, and zinc oxide are used for numerous applications. Silver nanoparticles, for example, are utilized due to their antimicrobial properties. Silver zeolites are used in beverage containers (EFSA Panel on FEC 2011). However, concerns are rising about the hazardous risks that these may have on human health, especially in terms of long-term effects (Magnuson et al. 2011; Sonkaria et al. 2012). To date, there is little information on the release of metals from nanomaterials, largely due to the fact that there are no requirements for disclosure of nanotechnology use and the failure of agencies to develop rigorous testing rules for specific applications. In Europe, for example, titanium nitride nanoparticles are intended to be used as an additive in polyethylene

terephthalate. In 2011 the European Food Safety Authority evaluated the safety of these nanoparticles and concluded that there is no safety concern for the consumer if the nanoparticulate substance used does not exceed 20 mg/kg for a particular application (EFSA Panel on FEC 2012).

In addition to applications in commercial products, nanotherapy aimed at using the chemical and physical characteristics of metallic nanomaterials for the treatment of infectious disease at the molecular level constitutes an active area of research. The small-sized particles are characterized by a high surface area, unique physicochemical properties, and surface charges which enhance their effective antimicrobial action (Weir et al. 2008). Antibacterial nanoparticles consisting of silver, gold, iron, zinc, copper, and titanium or their oxides have been featured in a number of studies and have been found to be effective against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and HIV virus (Sundar and Prajapati 2012). The antimicrobial mechanisms of nanomaterials are basically unknown but the commonly proposed pathogenic impacts are said to be dominated by inflammation-driven effects, including photocatalytic production of reactive oxygen species (which damage cellular and viral components), degradation of the bacterial cell wall or membrane, interruption of energy transduction, inhibition of enzyme activity, and DNA synthesis (Weir et al. 2008; Sundar and Prajapati 2012). Metal oxide nanoparticles have been shown to have different inflammatory footprints, implying different hazards in terms of pathology, risks, and risk severity (Chao et al. 2012). The availability of metals in nanoparticles is influenced by the zeta potential, solubility, the immune response associated with inflammation and hypoxic conditions, as well as degradation of macromolecules within inflammatory foci (Nizet and Johnson 2009; Chao et al. 2012). The limited information available suggests that current applications of metal-based nanomaterials can influence susceptibility to infectious diseases, judging by the effects of different metals on infective pathogens. Most of the studies relate to engineered nanomaterials, and there is currently little information on the effect of natural nanomaterials (“colloids”) on disease infection.

Emerging Metals

Emerging metals constitute another driver of change in metal exposure. Among the rare earth metals (Table 17.1), four deserve special attention relative to reported immune and/or microbial effects: cerium, gadolinium, lanthanum, and yttrium. Cerium has been reported to have both immunomodulatory and direct antimicrobial effects. Cerium nitrate has been used as an antibiofilm agent on hospital catheters and shown to significantly reduce biofilm formation by *Candida albicans* (Cobrado et al. 2013). Additionally, cerium helps to restore cell-mediated immunity among immunosuppressed burn patients (Peterson et al. 1985). Gadolinium chloride stimulates the innate immune system and, in particular, modulates macrophage cell population. It appears to signal through

TLR4 and TLR7 receptors on macrophages, increasing the production of several profibrotic or proinflammatory cytokines, chemokines, and growth factors (Wermuth and Jimenez 2012). However, pretreatment of rats with gadolinium chloride prior to bile duct ligation can also reduce Kupffer cell numbers and function in the liver as a means of reducing the risk of septic shock (Jones et al. 2013). Exposure of mice to lanthanum chloride inhibits production of proinflammatory (IL-1 and TNF- α) cytokines (Guo et al. 2011). The metal appears to act by inhibiting activation of NF-kappa B. Yttrium exposure has been reported to elevate humoral immunity while concomitantly producing a deficit of CD8+ T lymphocytes (Zhang et al. 2006b). Both traditional as well as comparatively new groups of metals (e.g., rare earth metals, titanium) contribute to this new category of human exposure. Information on immunomodulation relative to risk of infection by these compounds is becoming available (Appendix 17.1).

Direct Impacts of the Environment on Host–Parasite Interactions

From an ecological perspective, the processes by which metals in the environment could possibly impact host–pathogen interactions in a direct manner include (a) the changing pathogenicity of parasites and the emergence and spread of drug resistance and (b) changing of host resistance to the pathogen.

Metals and Drug Resistance in Bacteria

Antimicrobial resistant infections are considered the most critical global pathogenic threat to human health, according to recent reports by the WHO and Centers for Disease Control and Prevention. Newly emerging resistant strains are increasingly likely to be multidrug resistant (Jones et al. 2013). For this reason, identification of pressures that contribute to the dissemination of resistance is a high priority in biomedical and basic research.

Metals may be one source of pressure for resistance selection and dissemination. There is evidence for co-packaging of metal- and drug-resistant genes on transmissible genetic elements among bacteria (Baker-Austin et al. 2006). It has been suggested that environmental conditions of increased metal concentrations of both toxic and essential metals could contribute to the emergence and spread of drug resistance within environmental microbial systems (Bednorz et al. 2013). Specific to methicillin-resistant *S. aureus*, Cavaco et al. (2010) reported that cadmium and zinc drive co-selection for methicillin resistance in *S. aureus* through horizontal transfer of plasmids containing both *mec* and *czr* (Cd/Zn-resistance) genes. For this reason, there is increased concern that antimicrobial-resistance genes function as environmental pollutants (Martinez 2009).

Modification of Host Tolerance

The human host employs two nonmutually exclusive strategies in response to an infection: the ability to limit parasite burden (resistance) and the ability to limit the harm caused by a given burden of parasites (tolerance). From an ecological perspective, resistance protects the host at the expense of the parasite, whereas tolerance saves the host from harm without having any direct negative effects on the parasite (Ayres and Schneider 2012). This distinction is useful because it recognizes the important fact that hosts can sometimes be quite healthy despite high parasite burdens or, conversely, die with parasite loads that are tolerated by others; in fact, pathogen burden and health are not always well correlated (Schneider and Ayres 2008; Ayres and Schneider 2012; Medzhitov et al. 2012). Although these two components together determine how well a host is protected against the effects of parasitism, studies of human host defense have to date focused primarily on resistance; the possibility of tolerance and its implications have been largely ignored (Miller et al. 2006). The role that trace metal homeostasis might play in human tolerance mechanisms has been completely overlooked.

The mechanisms by which metal homeostasis increases the host's tolerance to invading pathogens have yet to be explored in detail. The following mechanisms may be involved:

- The production of reactive oxygen species and toxic free radicals.
- Inducible mechanisms such as the heme/HO-1 system (deficient for the *Hmox1* gene), which has been shown to provide tolerance for *Plasmodium* and polymicrobial infections (Seixas et al. 2009; Larsen et al. 2010) The expression of the Fe-sequestering protein ferritin H chain in mice and ferritin in humans has also been found to be associated with reduced tissue damage irrespective of pathogen burden (confer tolerance) following infection of mice with *Plasmodium* (Gozzelino et al. 2012).
- Activation of toll-like receptors, which can induce the production of cytoprotective and tissue repair factors to maintain epithelial integrity and homeostasis (Rakoff-Nahoum et al. 2004).
- Dietary imbalance in trace metal intake (Ayres and Schneider 2009).
- Phagocytosis-dependent microbial containment (Deretic and Levine 2009; Rashed 2011; Chifman et al. 2012).

When these and related mechanisms are sufficient to prevent major disruptions in physiological functions of the host after exposure to a parasite, infections remain asymptomatic.

The interaction of immune defense and tolerance mechanisms in protecting the human host against the pathophysiological effects of parasites has not been studied (Medzhitov et al. 2012). What is clear is that morbidity and mortality may result from the failure of tolerance mechanisms, even in the

presence of effective resistance. This would normally be indicated by hosts that present different morbidity or mortality profiles at comparative parasitemia. The distinction between failed resistance and failed tolerance is critically important in terms of the choice of therapeutic strategies. When failed tolerance is the underlying factor, boosting immunity and reducing pathogen burden (using drugs) may be ineffective, whereas enhancing tolerance (e.g., with trace metal intervention) may have salutary effects. Drug interventions that target the tolerance pathways may also be more desirable when immune defenses are either inefficient, compromised, or cause excessive immunopathology. Boosting tissue tolerance should be a particularly useful strategy in the case of pandemic diseases that cause morbidity and mortality worldwide, such as malaria, tuberculosis, and HIV—infectious diseases for which pathogen control through vaccination or antimicrobial drugs is currently unattainable (Medzhitov et al. 2012). Trace metal-related intervention holds some promise in this regard.

New Approaches to Epidemiological Studies

Whole-genome methods have led to the unprecedented discovery of robust associations between genetic markers and susceptibility to disease and have improved the understanding of infectious disease biology by revealing the crucial host–pathogen interaction sites (Khor and Hibberd 2012). Success in mapping the human genome and the realization that genetics can only account for a limited fraction of the etiology of diseases has led to the development of the complementary concept of the “exposome,” defined as the measure of all the exposures of an individual during a lifetime and how those exposures relate to health (Buck Louis and Sundaram 2012). Exposomics (the study of the exposome) focuses on simultaneous assessment of exposures that may originate from external and internal sources. External exposures may be from the environment, diet, or behavior, whereas internal environmental exposures stem from bodily functions and processes that govern homeostasis. Assessment of internal exposures focuses on chemicals and biomarkers and relies primarily on high-throughput molecular “omics” technologies: genomics, metabolomics, lipidomics, transcriptomics, and proteomics. Strategies in internal exposure assessment involve the use of (a) biomarkers to determine exposure, effect of exposure, disease progression, and susceptibility factors; (b) technologies that generate large amounts of data; and (c) advanced informatics to find statistical associations between exposures, effect of exposures, and other factors such as genetics with disease (Miller and Jones 2014). External exposures, in contrast, involve measurements related to environmental stressors using common approaches, such as survey instruments, geographic mapping and remote sensing technologies, direct reading instruments, personal exposure sensors, and laboratory-based analysis (Vrijheid et al. 2014). Exposomics thus

represents a new and exciting approach to improve, integrate, and consolidate exposure data for use in environment-wide association studies to identify associations between health outcomes and biomarkers of exposures, biomarkers of response, or patterns of disease.

Progress in the study of the nexus of trace metals and infectious diseases will clearly require new research paradigms for transforming how we think about exposures (internal and external), health, and disease; new research design; and new strategies for collecting and interpreting data. Exposome represents a good framework for assessing the effects of coexposure to metals and infective pathogens in that the paradigm is aimed at (a) accurate and reliable measurement of many exposures in the external environment, (b) measuring a wide range of biological responses in the internal environment, and (c) addressing the dynamic and life course nature of the exposure (Miller and Jones 2014). Exposome adopts a holistic approach to understanding the environmental determinants of disease, the mechanism by which these exposures interact with lifestyle behaviors, and delays in the manifestation of effects. Building the exposome for metals and pathologies of infectious diseases will require an integration of approaches, including environmental measurements and validated biomarkers. Below we propose approaches that could be used to address some of the major gaps in our knowledge of how metals impact on infectious disease within the exposome framework. We emphasize that many challenges still remain in developing the exposome concept into a workable approach for epidemiological research (Vrijheid et al. 2014).

Longitudinal and Cross-Sectional Studies in Areas with Overlapping Risks

Many parts of the world experience coincident exposures to trace metal deficiency/toxicity and endemic communicable diseases. High prevalence rates of As poisoning associated with high levels of arsenic in groundwater have been reported in many areas that have a high incidence of communicable diseases. Similar opportunities exist with respect to mercury (artisanal mining communities), lead (communities around base metal mining and smelting operations), and selenium (communities where soils are highly enriched in this element). The fact that soils with unusual concentrations of toxic metals are depleted in zinc and other microelements could provide an opportunity to explore the combined effects of Zn deficiency and toxic metal exposure on the pathogenesis of infectious diseases. Different types of study design offer the possibility of collecting exposure information from candidate communities:

- A cross-sectional study could be used to collect exposure data from a few people in great detail and determine what additional information is needed to validate hypothesized exposure-biomarker relationships.

- Case control studies could be used to look at exposures that have occurred relatively recently, when no relevant biologic samples may be particularly relevant.
- A cohort study (involving a group with a common set of characteristics over time) could be considered the gold standard in assessing exposure characteristics to ascertain the influence of metals on disease infection.

Inhalation Exposures to Toxic Metals and Infectious Disease

The lung is a unique microbiome for exposomic study. Real time modeling of exposure to airborne metals from pollutants using technologies that track the absorption and distribution of inhaled metals from airborne particulate matter within the body would give novel insights into how metals interact with the body and its microbiome at different interfaces. Data from such studies would provide information about how potentially toxic metals may influence respiratory and other infectious diseases.

Biomarkers that Provide Better Representation of Body Metal Status

Many of the body compartments that are sampled to provide estimates of body metal status do not indicate overall body metal status. As discussed earlier, these include, for example, blood, urine, hair, feces, sweat, and saliva. The “blood exposome” and its connection to disease was recently explored using human blood concentrations for 1,561 small molecules and metals along with their sources, evidence of chronic disease risks, and numbers of metabolic pathways (Rappaport et al. 2014). Similar studies could be done with the other biological samples. The resulting data could then be combined and metabolic profiling (metabonomics/metabolomics) used to define an individual’s metabolic phenotype, which is influenced by metal exposure, diet, lifestyle, genotype, and disease pathology; this could also reveal intermediate biomarkers for disease risk that reflect adaptive response to exposure. Implementation of such exposomic research will require the development and refinement of analytic methods capable of handling the diverse array of biomarkers and also other exposures for which there are no known or measurable biomarkers. Such analytic approaches can lead to a more comprehensive understanding of trace metal status in the context of environmental exposures and how changes in trace metal status relate to human health across the lifespan.

Use of Stable Isotopes to Study Uptake and Distribution of Metals by the Body over Time

In biomedical research, radioactive trace metals are first combined with other elements to form chemical compounds. The labeled compounds are taken internally, either orally or intravenously. Once administered to the patient (or

volunteer), the radioactive compounds are localized to specific organs or cellular receptors. This characteristic behavior makes it possible to determine the translocation of a metal to the infected organ(s) as well as to image the extent of a disease process in the body. Since these images are based on cellular function and physiology, rather than on physical changes in the tissue anatomy, they provide important insights on actual metabolic cycle and pharmacokinetics of an element. Radioisotopes can thus be used to assess the effect of disease state on systemic redistribution of a trace metal. A mass balance of the administered radionuclide can be used to estimate the bioavailability and absorption rate across the gastrointestinal tract. Because of concerns for health effects of the radionuclide, dietary exposure studies increasingly rely on stable isotopes of the elements. The diet (or food component) is spiked with a known stable isotope and the changes in the isotope fingerprint are monitored to estimate the excretion and bodily retention rates. This method has been used with success to estimate dietary exposure to zinc, lead, mercury, and other metals with more than one abundant stable isotope.

The identification of peptides that result from posttranslational modifications is important in understanding normal pathways of cellular regulation as well as assessing exposure and identifying damage from a toxic metal. Because of their low abundance in proteomes, effective detection of modified peptides by mass spectrometry typically requires enrichment to eliminate false identifications. Polacco et al. (2011) described a new method of high-resolution mass spectrometry for identifying peptides with Hg-containing adducts based on the influence of mercury's seven stable isotopes on peptide isotope distributions. They showed that the pattern of peak heights in isotope distributions from primary mass spectrometry single scans was able to identify Hg adducts with sensitivity and specificity greater than 90%. Summing peptide isotope distributions across multiple scans improved specificity to 99.4% and sensitivity above 95%, which made it possible to detect unexpected Hg modifications. Polacco et al. (2011) suggest that the method can also be used to detect several less common elements, including the essential element, selenium, as selenocysteine in peptides. This study and others with radioisotopes suggest that the isotopes of metals (radioactive or stable) can be an important tool ("isotopeomics") in exposome research. For a discussion on the application of isotopes for analysis of metal body distribution, see Maret et al. (this volume).

Conclusions

In this chapter we have tried to provide insights into current knowledge and gaps in understanding of the interplay between trace metals in the environment and disease infection. The contributions of metal deficiencies to the global burden of infectious diseases is substantial for zinc and iron but less defined for other metals. How emerging metals will relate to emerging pathogens, and

hence influence the disease burden, is a matter that deserves further research. Despite considerable research that is taking place separately on trace metals and infectious pathogens, little is currently known about the interactions between these two key determinants of health, especially in host microbiomes where direct coexposure occurs. A number of global trends have been identified that have the potential to upset the natural host–pathogen–metal nexus, including climate change, Western-style food processing, increasing reliance on infant formula, consumption of fast foods, and commercialization of products with metalliferous nanomaterials. From an ecological perspective, the two main processes by which the environment can directly impact host–pathogen interactions are (a) the changing pathogenicity of parasites with the emergence and spread of drug resistance and (b) the changing of host resistance to the pathogen. The specific mechanisms involved in each process are essentially unknown. In many parts of the world, the levels of trace metals in soils and local food chain are closely associated with the body burden of the metals and sometimes the health of local communities.

Failure to ascertain the environmental component of disease etiology stems, to a large extent, from limitations in our ability to assess the environmental exposures (which have traditionally been measured using questionnaires and geographical mapping) and tackle multiple exposures. A new exposure paradigm is needed that can integrate many external and internal exposures from different sources over the life course. Exposomics or environment-wide association studies offers one approach that can be used to gain a better handle on the environmental component essential to improving our understanding of the predictors, risk factors, and protective factors in complex interactions between trace metals, the environment, and infective pathogens. An understanding of the effects of such individual (and environmentally determined) exposomes on susceptibility to disease infection would be useful in developing appropriate intervention strategies to reduce burden of infectious diseases in many parts of the world.

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Appendix 17.1 Emission sources, selected applications, exposure pathways, and immune effects of elements. Exposure pathways: A, air (inhalation of contaminated air); F, food (consumption of contaminated food); W, water (drinking of water); T, tobacco (tobacco smoking); M, mouth (hand-to-mouth).

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Iron (Fe)	<i>Anthropogenic sources:</i> production of steel and iron, combustion of fossil fuels, production of cement, waste disposal, use of steel and iron <i>Natural sources:</i> reemission from soil and water surfaces, volcano eruptions	A, F, W	Both Fe deficiency and overload produce significant immune impairment and increased risk for certain categories of infections. Effective Fe homeostasis is critical in both macrophage function and Th balance. Th1 cells are more sensitive to suboptimal iron levels than Th2 cells (see Weiss, this volume)	Transferrin-based Fe supra-accumulation can starve bacteria and fungi Fe depletion also inhibits biofilm formation and enhances the activity of certain antibiotics Fe analogs, such as gallium, also interfere with bacteria enzyme function
Aluminum (Al)	<i>Anthropogenic sources:</i> Al production, various uses of aluminum, combustion of coal, waste disposal <i>Natural sources:</i> reemission from soil	A, F, W	Al targets primarily macrophages and T cells subchronic overload of AlCl ₃ suppresses spleen function Al adjuvants stimulate an inflammatory response which appears to produce adverse outcomes in susceptible individuals (e.g., macrophagic myofasciitis)	Aluminum oxide nanoparticles have demonstrated potential as antibacterial agents
Zinc (Zn)	<i>Sources:</i> Combustion of fuels, production of cement, non-ferrous and ferrous metals, waste incineration	A, F, W	Absence of Zn severely affects immune response; numerous investigations (e.g., Haase and Rink 2014) indicate not just a single function for zinc but a wide range of different roles	ZnO nano particles have antibiotic activity
Copper (Cu)	<i>Sources:</i> combustion of fuels, production of nonferrous and ferrous metals, waste incineration	A, F	Apoptotic reduction of CD4+ T cells Immunosuppression Oxidative damage and cellular depletion of lymphoid tissues Enhanced colonization by <i>Helicobacter pylori</i>	Cu(II) complexes of bis-thiosemicarbazones inhibit human <i>Neisseria gonorrhoeae</i>
Chromium (Cr)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W	Related to oxidative states and redox forms, Cr impairs lung host defenses against bacteria Induces allergic contact dermatitis	α -diimine Cr(III) complexes inhibit both Gram-positive and Gram-negative bacteria

Appendix 17.1 (continued)

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Manganese (Mn)	Sources: combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W	Mn enhances the release of inflammatory cytokines interleukin-6 and TNF- α from microglial cells that can promote the activation of astrocytes and subsequent release of inflammatory mediators such as prostaglandin E2 and nitric oxide	Insufficient information
Mercury (Hg)	Sources: fossil fuel combustion, artisanal Au mining and production, production of cement, nonferrous and ferrous metals, chlor-alkali, waste incineration	A, F, W	Immune bias toward Th2 responses Increased risk of viral infection-associated autoimmunity Potential to induce mast cell dysfunction Impairs immune development	Antibacterial properties probably via inhibited respiration
Lead (Pb)	Sources: combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W, M, T	Immune bias toward Th2 responses Inflammatory dysfunction Elevated risk of infection-related mortality among patients on maintenance hemodialysis	Antibacterial properties against select Gram-positive and Gram-negative bacteria
Cadmium (Cd)	Sources: combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W, T	Prenatal Cd disrupts signaling among thymocytes and reduces T cell numbers later in life Chronic exposure produces inflammatory dysfunction and risk of lung damage Promotes influenza virus proliferation by altering redox state	The composite, CdTe-TiO ₂ , exhibits antibacterial properties against both Gram-positive and Gram-negative bacteria
Arsenic (As)	Sources: combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W	CD4+ T cell-associated immunosuppression combined with elevated risk of innate immune driven-chronic inflammation Compromised airway barrier function and increased risk of respiratory infections	As(III)-containing Schiff bases display antibacterial activity against <i>Escherichia coli</i>

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Vanadium (V)	<i>Sources:</i> combustion of fuels, production of cement and nonferrous metals, waste incineration	A, F	Disrupted mucosal immunity Reduced thymic dendritic cell function Airway inflammation	V chloroperoxidase inhibits enterococcal biofilm formation.
Nickel (Ni)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W	Metal-associated hypersensitivity Potent activator of dendritic cells Signaling via the TLR 4 pathway	Antibacterial properties against select Gram-positive and Gram-negative bacteria
Antimony (Sb)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F	Pentavalent antimony complexes activate macrophages for ROS and NO attack against parasites	Antimony is a preferred agent against leishmaniasis, probably acting in concert with immune effects
Selenium (Se)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F	Deficiency increases risk of certain viral, bacterial, and parasitic infections Increase risk of organ pathology and failure	Organoselenium inhibits the formation of certain bacterial biofilms
Molybdenum (Mo)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F	Enhanced protection against the nematode parasite <i>Trichostrongylus colubriformis</i> Higher levels produce apoptosis and compromise lymphoid tissue architecture	Antibacterial properties against select Gram-positive and Gram-negative bacteria
Beryllium (Be)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F	Induction of airway granulomatous inflammation via innate immune cells, Th1-directed responses, and a dysfunctional dysfunctional CTLA-4 pathway Increase respiratory infections associated with chronic beryllium disease	Insufficient information
Gallium (Ga)	<i>Sources:</i> Al production, nonferrous metal (mostly Zn) production, combustion of coal	A, F	Gallium arsenide impairs macrophage antigen processing and produces both local inflammation and system immunosuppression Gallium nitrate can restrict the growth of <i>Mycobacterium tuberculosis</i> inside macrophages and protect the lung	Gallium interferes with Fe metabolism and has both bacteriostatic and bactericidal properties Gallium nitrate has antibacterial activity against <i>Rhodococcus equi</i>

Appendix 17.1 (continued)

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Cobalt (Co)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration	A, F, W	Co-alloy particles can trigger innate immune response via the TLR4 signaling pathway Potent activator of dendritic cells Cobalt protoporphyrin reduces the macrophage burden of <i>Trypanosoma cruzi</i> during infection	Cobalt Schiff base complexes possess broad-spectrum antibacterial activity Certain Co(II) complexes have activity against <i>M. tuberculosis</i>
Tin (Sn)	<i>Sources:</i> combustion of fuels, production of cement, nonferrous and ferrous metals, waste incineration, various uses	A, F, W	Organotinins (e.g., tributyltin) cause thymic atrophy and apoptosis of immune cells Suppression of both humoral and cell-mediated immunity result including reduced host defense against bacteria.	SnO ₂ nanostructures exhibit surfactant-promoted antibacterial activity SnO ₂ nanowires inhibit herpes simplex-1 infection Certain Sn complexes exhibit anti-leishmanial activity
Gold (Au)	<i>Use:</i> jewelry, photography, electrical appliances, electronics, satellites	A, F	Associated with potential autoimmunity involving mast cell dysfunction Au salts can be allergic sensitizers	Anti-leishmanial activity of Au nanoparticles Antibacterial biofilm activity of Au nanocomposites
Silver (Ag)	<i>Use:</i> color and stained steel, coins, ornaments, jewelry, electrical appliances, catalyzers, cables, wires, mirrors	F	Potential promoter of autoimmunity in susceptible populations May involve mast cell dysfunction	Antibacterial action against Gram-negative bacteria Anti-leishmanial activity of Ag nanoparticles Biofilm inhibition of Ag nanocomposites
Boron (B)	<i>Use:</i> dopant in semiconductor industry, sodium perborate in bleaching, borax component in fiberglass, in glass and ceramics, reagents in chemical industry	F, W	Benzoxaborole analogs inhibit proinflammatory cytokine responses via inhibition of toll-like receptor signaling	Several B-containing antibacterials inhibit Gram-negative bacteria via inhibition of bacterial leucyl tRNA synthetase
Thallium (Tl)	<i>Use:</i> optics, electronics, superconductivity, medical applications	F	Insufficient information	Insufficient information

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Uranium (U)	<i>Use:</i> nuclear reactors, colorant in glass	F, W	Immune bias toward Th2 responses with reduced antimicrobial function of macrophages	
Platinum (Pt)	<i>Use:</i> catalysts, electronics, glass industry, dentistry, jewelry	A, F	Pt chemotherapeutics enhance dendritic cell activity via a STAT-6 pathway Hypersensitivity reactions are common.	Pd complexes of polyamides containing sulfones have antifungal and antibacterial activity
Palladium (Pd)	<i>Use:</i> catalysts, electronics, glass industry, dentistry, jewelry	A, F	Reported respiratory and dermatological sensitizer Causes occupational asthma Causes some Th-associated cytokine alterations both <i>in vitro</i> and <i>in vivo</i>	Greater inhibitory activity of Pd nanoparticles against <i>Staphylococcus aureus</i> than toward <i>E. coli</i>
Rhodium (Rh)	<i>Use:</i> catalysts, electronics, glass industry, dentistry, jewelry	A, F	Reported to cause allergic contact dermatitis	Rh-metal complexes have reported antityranosome activity
Scandium (Sc)	<i>Use:</i> light Al-Sc alloys for aerospace components, additive in metal-halide lamps and Hg vapor lamps, radioactive tracing agent in oil refineries	F	Insufficient information	A component of laser treatments that has shown antibacterial activity
Yttrium (Y)	<i>Use:</i> yttrium aluminum garnet laser, yttrium vanadate as host for europium in TV red phosphor, high-temperature superconductors, Y-stabilized zirconia, yttrium iron garnet microwave filters, energy-efficient light bulbs, spark plugs, gas mantles, additive to steel	F	Elevates components of humoral immunity while concomitantly producing a deficit of CD8+ T lymphocytes	Yttrium fluoride nanoparticles inhibit colonization by <i>E. coli</i> and <i>S. aureus</i> Y(III) complex containing 1,10-phenanthroline as a ligand has shown antibacterial activity
Lanthanum (La)	<i>Use:</i> high refractive index and alkali-resistant glass, flint, hydrogen storage, battery-electrodes, camera lenses, fluid catalytic cracking catalyst for oil refineries	F	Inhibits innate immune cell production of pro-inflammatory cytokines upon bacterial stimulation	Lanthanum calcium manganate is inhibitory for <i>Pseudomonas aeruginosa</i> La nanoparticles may have application as a phosphate starvation strategy against bacteria

Appendix 17.1 (continued)

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Cerium (Ce)	<i>Use:</i> oxidizing agent, polishing powder, yellow colors in glass and ceramics, catalyst, ferro-cerium flints for lighters	F	Cerium oxide nanoparticles accelerate wound healing	Cerium nitrate has been used as an antibiofilm agent on hospital catheters
Praseodymium (Pr)	<i>Use:</i> magnets, lasers, core material for carbon arc lighting, colorant in glasses and enamels, additive in didymium glass, ferro-cerium fire-steel (flint) products.	F	Insufficient information	Insufficient information
Neodymium (Nd)	<i>Use:</i> magnets, lasers, violet colors in glass and ceramics, didymium glass, ceramic capacitors	F	Insufficient information	Incorporated into some antibacterial nanoparticles
Promethium (Pm)	<i>Use:</i> nuclear batteries	F	Insufficient information	Insufficient information
Samarium (Sm)	<i>Use:</i> magnets, lasers, neutron capture, masers	F	¹⁵³ Sm leixidronam used in stem cell transplantation with no drug-attributed adverse effects	Sm(III) ions enhance the antimicrobial activity of enrofloxacin.
Europium (Eu)	<i>Use:</i> red and blue phosphors, lasers, mercury-vapor lamps, fluorescent lamps, NMR relaxation agent	F	Insufficient information	Used for imaging of antimicrobials
Gadolinium (Gd)	<i>Use:</i> magnets, high refractive index glass or garnets, lasers, X-ray tubes, computer memories, neutron capture, MRI contrast agent, NMR relaxation agent, magnetostrictive alloys, steel additive	F	Targets macrophage cell populations possibly with signaling via TLR receptors Specifically depletes Kupffer cells	Insufficient information

Element	Major Atmospheric Emission Sources and Select Applications	Exposure Pathways	Effects on Immune System and Host Defenses Against Infection	Direct Antimicrobial Properties
Terbium (Tb)	<i>Use:</i> green phosphors, lasers, fluorescent lamps, magnetostrictive alloys	F	Insufficient information	Insufficient information
Dysprosium (Dy)	<i>Use:</i> magnets, lasers, magnetostrictive alloys	F	Insufficient information	Dy(III) complex containing 1,10-phenanthroline (phen), [Dy(phen) ₂ (OH) ₂ Cl] ₂ ·H ₂ O has antibacterial activity via bacterial DNA binding
Holmium (Ho)	<i>Use:</i> lasers, wavelength calibration standards for optical spectrophotometers, magnets	F	Used in lasers for anti-inflammation (e.g., arthritis) treatments	A series of Ho(III) complexes have reported activity against <i>S. aureus</i>
Erbium (Er)	<i>Use:</i> infrared lasers, vanadium steel, fiber-optic technology	F	Associated laser phototherapy appears to promote gingival wound healing	Associated with laser phototherapy against herpes simplex virus infections as well as root canal-associated <i>Candida albicans</i> infections
Thulium (Tm)	<i>Use:</i> portable X-ray machines, metal-halide lamps, lasers	F	Insufficient information	Insufficient information
Ytterbium (Yb)	<i>Use:</i> infrared lasers, chemical reducing agent, decoy flares, stainless steel, stress gauges	F	Insufficient information	Yb(III) complexes have antibacterial activity via DNA binding
Lutetium (Lu)	<i>Use:</i> scan detectors, high refractive index glass, lutetium tantalate hosts for phosphors	F	Insufficient information	Lu(III) complexes have reported antibacterial activity

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