CHAPTER 4
HUMAN HEALTH AND HEAVY METALS EXPOSURE
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Metals, a major category of globally-distributed pollutants, are natural elements that have been extracted from the earth and harnessed for human industry and products for millenia. (An exception to metals being "natural" is plutonium, the material at the heart of nuclear weapons, created by man through the processing of uranium.) Metals are notable for their wide environmental dispersion from such activity; their tendency to accumulate in select tissues of the human body; and their overall potential to be toxic even at relatively minor levels of exposure. Some metals, such as copper and iron, are essential to life and play irreplaceable roles in, for example, the functioning of critical enzyme systems. Other metals are *xenobiotics*, i.e., they have no useful role in human physiology (and most other living organisms) and, even worse, as in the case of lead and mercury, may be toxic even at trace levels of exposure. Even those metals that are essential, however, have the potential to turn harmful at very high levels of exposure, a reflection of a very basic tenet of toxicology--"the dose makes the poison." One reflection of the importance of metals relative to other potential hazards is their ranking by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), which lists all hazards present in toxic waste sites according to their prevalence and the severity of their toxicity. The first, second, third, and sixth hazards on the list are heavy metals: lead, mercury, arsenic, and cadmium, respectively.

Exposure to metals can occur through a variety of routes. Metals may be inhaled as dust or fume (tiny particulate matter, such as the lead oxide particles produced by the combustion of leaded gasoline). Some metals can be vaporized (e.g., mercury vapor in the manufacture of fluorescent lamps) and inhaled. Metals may also be ingested involuntarily through food and drink. The amount that is actually absorbed from the digestive tract can vary widely, depending on the chemical form of the metal and the age and nutritional status of the individual. Once a metal is absorbed, it distributes in tissues and organs. Excretion typically occurs primarily through the kidneys and digestive tract, but metals tend to persist in some storage sites, like the liver, bones, and kidneys, for years or decades.

The toxicity of metals most commonly involves the brain and the kidney, but other manifestations occur, and some metals, such as arsenic, are clearly capable of causing cancer. An individual with metals toxicity, even if high dose and acute, typically has very general symptoms, such as weakness or headache. This makes the diagnosis of metals toxicity in a clinical setting very difficult unless a clinician has the knowledge and training to suspect the diagnosis and is able to order the correct diagnostic test. Chronic exposure to metals at a high enough level to cause chronic toxicity effects (such as hypertension in individuals exposed to lead and renal toxicity in

individuals exposed to cadmium) can also occur in individuals who have no symptoms.

Much about metals toxicity, such as the genetic factors that may render some individuals especially vulnerable to metals toxicity, remains a subject of intense investigation. It is possible that low-level metals exposure contributes much more towards the causation of chronic disease and impaired functioning than previously thought.

This chapter focuses on exposure to the four "heavy" metals on the ATSDR list mentioned above —lead, mercury, arsenic, and cadmium—as they are arguably the most important metal toxins from a global, as well as U.S. perspective. Some additional remarks are also made regarding a few other metals of concern. (Exposure to arsenic and lead in drinking water is covered by John Balbus in Chapter 3, Water Quality and Water Resources.)

Lead

Exposure

For centuries, lead has been mined and used in industry and in household products. Modern industrialization, with the introduction of lead in mass-produced plumbing, solder used in food cans, paint, ceramic ware, and countless other products resulted in a marked rise in population exposures in the 20th century.

The dominant source of worldwide dispersion of lead into the environment (and into people) for the past 50 years has clearly been the use of lead organic compounds as antiknock motor vehicle fuel additives. Since leaded gasoline was introduced in 1923, its combustion and resulting contamination of the atmosphere has increased background levels everywhere, including the ice cap covering Northern Greenland (Fig. 1), where there is no industry and few cars and people.[1] Although a worldwide phase-out of leaded gasoline is in progress (see http://www.earthsummitwatch.org/gasoline.html for details), it is still being used all over the world.

The current annual worldwide production of lead is approximately 5.4 million tons and continues to rise. Sixty percent of lead is used for the manufacturing of batteries (automobile batteries, in particular), while the remainder is used in the production of pigments, glazes, solder, plastics, cable sheathing, ammunition, weights, gasoline additive, and a variety of other products. Such industries continue to pose a significant risk to workers, as well as surrounding communities.

In response to these risks, many developed countries over the last 25 years have implemented regulatory action that has effectively decreased actual exposures to the general population. However, exposures remain high or are increasing in many developing countries through a rapid increase in vehicles combusting leaded gasoline and polluting industries (some of which have been "exported" by corporations in developed countries seeking relief from regulations). Moreover, some segments of the population in developed countries (such as the U.S.) remain at high risk of exposure because of the persistence of lead paint, lead plumbing, and lead-contaminated soil and dust, particularly in areas of old urban housing.

A number of factors can modify the impact of lead exposures. For example, water with a lower pH (such as drinking water stemming from the collection of untreated "acid rain") will

leach more lead out of plumbing connected by lead solder than more alkaline water.[2] Lead from soil tends to concentrate in root vegetables (e.g., onion)[3] and leafy green vegetables (e.g., spinach). Individuals will absorb more lead in their food if their diets are deficient in calcium, iron, or zinc.[4] Other more unusual sources of lead exposure also continue to be sporadically found, such as improperly glazed ceramics, lead crystal, imported candies, certain herbal folk remedies, and vinyl plastic toys.

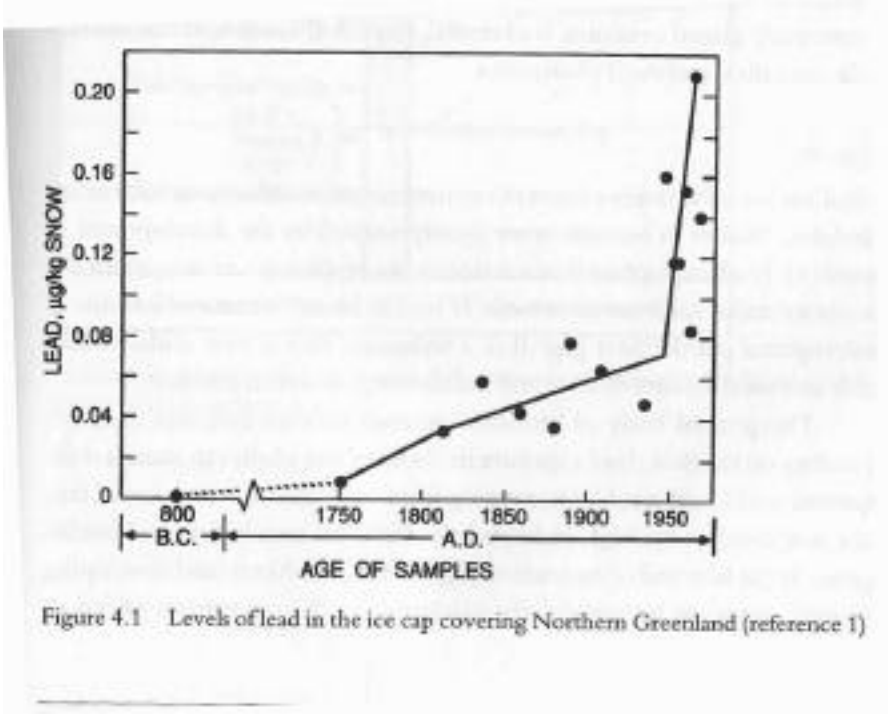

Figure 4.1 Levels of lead in the ice cap covering Northern Greenland (reference 1)

Toxicity

Lead has been the intense focus of environmental health research for many decades. Studies in humans were greatly assisted by the development of methods (such as graphite furnace atomic absorption spectroscopy) for the accurate and reliable measurement of lead in blood (measured in units of micrograms per deciliter [µg/dL]), a technique that is now widely available and used for surveillance and monitoring, as well as research.

The general body of literature on lead toxicity indicates that, depending on the dose, lead exposure in children and adults can cause a wide spectrum of health problems, ranging from convulsions, coma, renal failure, and death at the high end to subtle effects on metabolism and intelligence at the low end of exposures.[5] (Fig. 2) Children (and developing fetuses) appear to be particularly vulnerable to the neurotoxic effects of lead. A plethora of well-designed prospective epidemiologic studies has convincingly demonstrated that low-level lead exposure in children less than five years of age (with blood lead levels in the 5-25 µg/dL range) results in deficits in intellectual development as manifested by lost intelligence quotient points.[6] As a result, in the U.S., the Centers for Disease Control (CD) lowered the allowable amount of lead in a child's blood from 25 to 10 µg/dL and recommended universal blood lead screening of all children

between the ages of six months and five years.[7] (For more details, see http://www.cdc.gov/nceh/lead/lead.htm.)

However, a number of issues still remain unresolved with respect to lead toxicity in children. Among the most important is the risk posed to the fetus posed by mobilization of long-lived skeletal stores of lead in pregnant women.[8] Recent research has clearly demonstrated that maternal bone lead stores are mobilized at an accelerated rate during pregnancy and lactation[9] and are associated with decrements in birth weight, growth rate, and mental development.[10-12] Since bone lead stores persist for decades,[13] it is possible that lead can remain a threat to fetal health many years after environmental exposure had actually been curtailed.

In contrast to children, adults are generally allowed by regulations to be exposed to higher amounts of lead. In the U.S., for example, the Occupational Safety and Health Administration requires that the blood lead levels of exposed workers be maintained below 40 μg/dL as a way of preventing toxic effects to nerves, the brain, kidney, reproductive organs, and heart. (For more information, see http://www.osha-slc.gov/OshStd_data/ 1910_1025_APP_C.html.) This standard is probably outdated, however. First, the standard does not protect the fetuses of women who become pregnant while on the job (or even if they leave the job for several years because of the issue of bone lead mobilization, as discussed above). Second, recent epidemiologic studies have linked blood lead levels in the range of 7-40 μg/dL with evidence of toxicity in adults, such as neurobehavioral decrements[14] and renal impairments.[15] Third, recent studies using a newly developed technique, K-x-ray fluorescence, to directly measure bone lead levels (as opposed to blood lead levels) have provided evidence demonstrating that cumulative lead exposure in individuals with blood lead levels well below 40 μg/dL is a major risk factor for the development of hypertension,[16-18] cardiac conduction delays,[19] and cognitive impairments.[20,21]

Finally, even as research progresses to delineate the full toxicologic implications of lead exposure, investigations at the interface of genetics and environmental health are beginning to uncover subgroups of individuals who may be particularly susceptible to the toxicity of lead.[22]

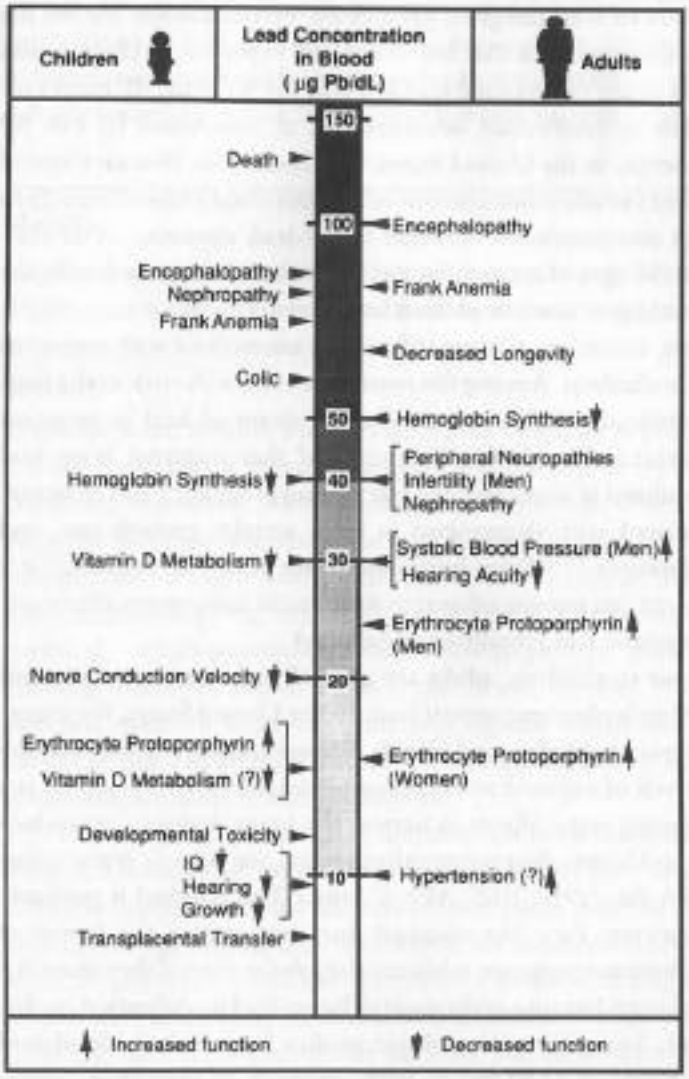

Figure 4.2 Health effects associated with various levels of lead in the blood of children and adults (reference 2)

Mercury

Exposure

Mercury comes in a number of different chemical forms. Metallic mercury (Hg^o) is used in thermometers, dental amalgams, and some batteries. In its pure form, metallic mercury is a liquid. Contrary to popular opinion, it is not hazardous if ingested (as it is not significantly absorbed in this form). However, if left standing, or even worse, if aerosolized, for example, through attempted vacuum cleaning, metallic mercury will volatilize into a vapor that is well absorbed by the lungs. Mercurous and mercuric mercury (Hg^+ and Hg^{2+} , respectively) are encountered in some chemical, metal-processing, electrical-equipment, automotive, and building industries and in

medical and dental services. Mercurous and mercuric mercury form inorganic and organic compounds with other chemicals that can be readily absorbed through ingestion. All three forms of mercury are toxic to various degrees.

From a global perspective, mercury has been increasing in importance as a widespread contaminant. About half of the National Priority List toxic waste sites in the U.S. contain mercury. Mercury dispersion through atmospheric deposition has increased markedly through waste incineration; ironically, the medical industry is one of the largest contributors to mercury pollution in this fashion.[23] Some countries, such as Brazil, have seen widespread mercury contamination (and resultant health effects) through a combination of its indiscriminate use in gold mining and deforestation.[24] When deposited in soil, organic mercury compounds are slowly broken down into inorganic compounds; conversely, inorganic mercury can be converted by microorganisms in soil and water into the organic compound methyl mercury, which is then bioconcentrated up the food chain. Fish, particularly tuna, king mackerel, and swordfish, can concentrate methyl mercury at high levels. Their consumption, though popular, should be limited in frequency (e.g., to less than twice per week) and entirely avoided by women during pregnancy.

Toxicity

High levels of mercury exposure that occur through, for example, inhalation of mercury vapors generated by thermal volatilization can lead to life-threatening injuries to the lungs and neurologic system. At lower but more chronic levels of exposure, a typical constellation of findings arises, termed *erethism*—with tremor of the hands, excitability, memory loss, insomnia, timidity, and sometimes delirium—that was once commonly seen in workers exposed to mercury in the felt-hat industry ("mad as a hatter"). Even relatively modest levels of occupational mercury exposure, as experienced, for example, by dentists, have been associated with measurable declines in performance on neurobehavioral tests of motor speed, visual scanning, verbal and visual memory, and visuomotor coordination.[25] Contrary to some opinions expressed in the popular media, however, evidence from well-conducted studies is lacking that the small amount of mercury released from dental amalgams during chewing is capable of causing significant illnesses, such as mutliple sclerosis, systemic lupus, or chronic fatigue syndrome.[26] Special note should be taken of dimethylmercury---a "supertoxic, superdangerous" compound that can penetrate through latex gloves, as well as skin. Exposure to only a few drops can lead to central nervous system degeneration and death,[27] but the compound is luckily encountered only in specialized laboratories.

Of greatest concern on a global scale is the sensitivity of the fetal and infant nervous system to low-level mercury toxicity. Mothers exposed to mercury in the 1955 disaster in Minamata Bay, Japan, gave birth to infants with mental retardation, retention of primitive reflexes, cerebellar symptoms, and other abnormalities. Recent research in the Faroe Islands has demonstrated that, even at much lower levels, mercury exposure to pregnant women through dietary intake of fish and whale meat, an important regional food staple, is associated with decrements in motor function, language, memory, and neural transmission in their offspring.[28,29] Organic mercury, the form of mercury bioconcentrated in fish and whale meat, readily crosses the placenta and appears in breast milk.

Arsenic

Exposure

Significant exposure to arsenic occurs through both anthropogenic and natural sources. Occupational and community exposures to arsenic from the activities of humans occur through the smelting industry, the use of gallium arsenide in the microelectronics industry, and the use of arsenic in common products such as wood preservatives, pesticides, herbicides, fungicides, and paints. Widespread dispersion of arsenic is a byproduct of the combustion of fossil fuels in which arsenic is a common contaminant. Arsenic continues to be found in some folk remedies.

In some areas of the world, arsenic is also a natural contaminant of wells. Deep-water wells in parts of Taiwan and Chile are now well-known to be contaminated with arsenic, giving rise to chronic manifestations of toxicity discussed below.[30,31] Water from relatively shallow tube wells that were placed in areas of Bangladesh, West Bengal, and other parts of the subcontinent has also been recently found to be heavily contaminated with arsenic[32]—a particularly unfortunate revelation given the dire need for potable drinking water in the populations living in these areas. Water in some parts of the U.S., such as areas of the Southwest, also carry a significant risk of arsenic contamination. (See Chapter 3.)

Toxicity

The toxicity of an arsenic-containing compound depends on its valence state (zero-valent, trivalent, or pentavalent), its form (inorganic or organic), and factors that modify its absorption and elimination. Inorganic arsenic is generally more toxic than arsenic, and trivalent arsenite is more toxic than pentavalent and zero-valent arsenic. These nuances are important. For example, testing biological samples for arsenic in an individual with suspected toxicity must be done more than 48 hours after the individual abstains from eating seafood; otherwise, the test may be confounded by the presence of arsenobentaine, a relatively harmless form of arsenic that is contained in fish at high levels of concentration.

Once absorbed into the body, arsenic undergoes some accumulation in soft tissue organs such as the liver, spleen, kidneys, and lungs, but the major long-term storage site for arsenic is keratin-rich tissues, such as skin, hair, and nails---making the measurement of arsenic in these biological specimens useful for estimating total arsenic burden and long-term exposure under certain circumstances.

Acute arsenic poisoning is infamous for its lethality, which stems from arsenic's destruction of the integrity of blood vessels and gastrointestinal tissue and its effect on the heart and brain. Chronic exposure to lower levels of arsenic results in somewhat unusual patterns of skin hyperpigmentation, peripheral nerve damage manifesting as numbness, tingling, and weakness in the hands and feet, diabetes, and blood vessel damage resulting in a gangrenous condition affecting the extremities.[33] Chronic arsenic exposure also causes a markedly elevated risk for developing a number of cancers, most notably skin cancer, cancers of the liver

(angiosarcoma), lung, bladder, and possibly the kidney and colon. The dose necessary to increase the risk for cancer has recently become the focus of particularly intense scrutiny in the U.S. because of proposed efforts to lower standards governing general populations exposures to arsenic. Among environmental scientists studying this problem, the most common view is that the current standard for the allowable amount of arsenic in U.S. drinking water—50 μg/liter—is probably not adequate to sufficiently safeguard the general population from arsenic's cancer risk.[34]

Cadmium

Exposure

Cadmium exposure is encountered in industries dealing with pigment, metal plating, some plastics, and batteries. Cadmium pollution (e.g., the emissions of a cadmium smelter or industry and the introduction of cadmium into sewage sludge, fertilizers, and groundwater) can result in significant human exposure to cadmium through the ingestion of contaminated foodstuffs, especially grains, cereals, and leafy vegetables. Airborne cadmium exposure is also a risk posed by the incineration of municipal waste containing plastics and nickel-cadmium batteries. Cigarette smoking constitutes an additional major source of cadmium exposure.

Toxicity

The health implications of cadmium exposure are exacerbated by the relative inability of human beings to excrete cadmium. (It is excreted but then re-absorbed by the kidney.) Acute high-dose exposures can cause severe respiratory irritation. Occupational levels of cadmium exposure are a risk factor for chronic lung disease (through airborne exposure) and testicular degeneration[35] and are still under investigation as a risk factor for prostate cancer.[36] Lower levels of exposure are mainly of concern with respect to toxicity to the kidney. Cadmium damages a specific structure of the functional unit of the kidney (the proximal tubules of each nephron) in a way that is first manifested by leakage of low molecular weight proteins and essential ions, such as calcium, into urine, with progression over time to frank kidney failure.[37] This effects tends to be irreversible,[38] and recent research suggests that the risk exists at lower levels of exposure than previously thought.[39,40] Even without causing frank kidney failure, however, cadmium's effect on the kidney can have metabolic effects with pathologic consequences. In particular, the loss of calcium caused by cadmium's effect on the kidney can be severe enough to lead to weakening of the bones. "Itai-itai" disease, an epidemic of bone fractures in Japan from gross cadmium contamination of rice stocks, has recently been shown to happen in more subtle fashion among a general community living in an area of relatively modest cadmium contamination.[41] Increased cadmium burden in this population was found to be predictive of an increased risk of bone fractures in women, as well as decreased bone density and height loss (presumably from the demineralization and compression of vertebrae) in both sexes.

Other Metals of Concern

Manganese has recently become a metal of global concern because of the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive. Proponents of the use of MMT have claimed that the known link between occupational manganese exposure and the development of a Parkinson's disease-like syndrome of tremor, postural instability, gait disorder, and cognitive disorder has no implications for the relatively low levels of manganese exposure that would ensure from its use in gasoline. However, this argument is starkly reminiscent of the rationale given for adding lead to gasoline, and what little research that exists from which one can infer the toxicity potential of manganese at low-levels of exposure is not particularly comforting.[42]

Aluminum contributes to the brain dysfunction of patients with severe kidney disease who are undergoing dialysis. High levels of aluminum have been found in neurofibrillary tangles (characteristic brain lesions in patient's with Alzheimer's disease), as well as in the drinking water and soil of areas with an unusually high incidence of Alzheimer's disease. Nevertheless, the experimental and epidemiologic evidence for a causal link between aluminum exposure and Alzheimer's disease is, overall, relatively weak. More research is needed on this topic, since general population exposures to aluminum are increasing through the use of aluminum cookware, aluminum-containing deodorants, and other products.

Chromium, in its hexavalent form, which is the most toxic species of chromium, is used extensively in some industries such as leather processing. As a result, chromium has become a major factory run-off pollutant that is beginning to become a global trend. The toxicity of chromium stems from its tendency to be corrosive and to cause allergic reactions. **[The last sentence was reworked; is it okay?]** Chromium is a carcinogen, particularly of the lung through inhalation.

Critical Prescriptions

Lead has been emphasized in this review because, in many ways, lead is the archetype metal toxin in terms of its many sources and pathways for exposure, global distribution, ability to accumulate in the body, and impact on human health even at low levels of exposure. Unfortunately, even though lead is arguable the most-studied toxin in all of environmental health, there still remains a host of unresolved issues, such as whether and to what degree certain sub-populations are especially susceptible to lead toxicity (through genetic variations), to what degree lead's effect on mental development in children is reversible, and whether lead plays a role in the development of chronic neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The number of unresolved issues surrounding the other toxic metals of concern is only larger. Nevertheless, even without additional basic research into the toxicity of metals, enough is known to warrant close attention to and efforts at controlling metals contamination.

Prescriptions

Prescription #1: Accelerate and complete the global phase-out of leaded gasoline. Some countries, like Italy, Greece, Spain, Australia, and Chile, lag behind in their switch to unleaded gasoline; others, such as South Africa, Nigeria, the Confederation of Independent States, Israel,

and Malaysia, have yet to even commit to this process. (see http://www.earthsummitwatch.org/gasoline.html for more details.) Delays are inadvisable, given the accumulation of knowledge on low-level lead toxicity reviewed above.

Prescription #2: Begin an Effort to Monitor Levels and Trends in Metals Pollution World-Wide.
Currently, no agency or database exists from which one can gain a clear sense of levels and trends in pollution by metals. Some monitoring occurs in the use and distribution of exposure vectors---such as worldwide trends in the use of leaded gasoline (see above), but the sources of exposure to metals are diverse and numerous, making it difficult to infer the impact of such exposure vector trends on exposure at the individual level. A clearer picture would emerge if samples were regularly taken, using standardized methods for sampling and analysis, of metal levels in air, drinking water, and market basket surveys of food.

Prescription #3: Establish Population-Based Biomonitoring for Selected Metals.
Exposure to some metals, such as lead, can be best monitored by following trends in blood or other media (such as urine). Many such surveys appear regularly in the literature, but they are haphazard and depend on the specific (and changing) interests of their sponsors. The principal challenges to establishing such a system are defining test populations that are fairly representative of national/regional trends, standardizing technical protocols for analysis of samples, and organizing and funding such an effort.

Prescription #4: Educate Governments, Scientists, and the General Public about the Toxicity of Metals
The information above, while in the public domain, is not easily accessed or grasped by average citizens and policy-makers and rarely taught in schools of medicine, nursing, or other allied health professions.

Prescription #5: Declare a Moratorium on the Production, Distribution, and Use of Products that are Likely to Significantly Increase Global Exposure to Toxic Metals
The most obvious target for this prescription is the example of methylcyclopentadienyl manganese tricarbonyl (MMT), the newly created additive for gasoline. It makes little sense to globally disperse a new metal for which the toxicologic implications are not fully known (or, in the case of MMT, known to be severe at high levels of exposure).

Prescription #6: Continue Basic Research into the Impact of Metals on Human Health
As described in various places earlier in this chapter, numerous unresolved issues remain regarding the impact of metals on human health. Current research priorities (and funding) in medical research is heavily skewed towards treatment of chronic diseases such as cancer, heart disease, neurologic diseases, and osteoporosis. Attention should be increased towards research on prevention, the most fundamental aspect of which is investigating the causes and relative importance of various risk factors for the diseases of interest.

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