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Heavy metals as risk factors for human diseases – a Bayesian network approach

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Abstract. – Modern industrial agricultural processes expose human beings to multifactorial environmental pollution including heightened levels of heavy metals. The effects of acute heavy metal exposures at toxic levels are usually known; they are tested for and treated promptly. The effects of low/moderate-level chronic heavy metal exposures are less known as they may be subclinical, and pathogenic effects may only manifest clinically over time under the disguise of a diagnosable disease or miscellaneous symptoms attributed to aging. Consequently, the health impact of low-moderate heavy metal exposure is unlikely to be identified. Furthermore, established heavy metal safety levels often fail to recognize the potential toxic effects on humans.

We report in this review what is known about the sub-chronic and chronic effects of exposure to heavy metals, particularly lead, mercury, cadmium, arsenic, and nickel, and we highlight their possible effects in the brain, cardiovascular and endocrine-metabolic systems, and on reproduction.

Key Words:
Heavy metal, Essential mineral, Arsenic, Cadmium, Lead, Mercury, Nickel, Brain, Neurodegenerative disorders, Alzheimer's disease, Mental disorders, Type 2 diabetes, Hypertension, Cardiovascular disease, Thyroid, Infertility, Bone, Parkinson, Depression, Anxiety, Attention deficit hyperactivity disorder, Cognitive, Cognition, Exposure, Toxic, Zinc, Selenium, Antioxidant, Testis, Uterus, Pituitary, Calcium, Manganese, Bayesian network, Glutathione, Free radical.

Introduction

Industrial processes, advanced farming, and agricultural processes have exposed humans to increased environmental pollution in the air, soil[1], land water[2], sea water[3], and fresh water[4]. This contamination includes increased levels of heavy metals (HMs) in polluted air, water[5,6], soil[1], and food[7]. HMs (e.g., mercury, lead, cadmium) are so defined due to their higher atomic weight and specific density, five times that of water. Acute high-level exposure to HMs causes overt clinical toxicity and may be detected quickly due to the rapid health deterioration they can cause. Thus, while the effects of acute HM exposure at toxic levels are usually known, low-to-moderate chronic level exposure to HMs may trigger more insidious biological and clinical toxicities on health over time[8]. The negative impacts of these clinical toxicities on health are gradual and subtle, and thus often attributed – erroneously and in good faith – by subjects and physicians to physiological aging, and/or may manifest as a diagnosable chronic aging disorder [e.g., hypertension (HTN), type 2 diabetes (T2D)]. Consequently, the root cause of the disease or symptoms often goes uninvestigated and unidentified.

Of interest, HM toxic effects are synergistic rather than additive[9]. In fact, each HM can biologically disrupt the contaminated organism and act synergistically with other HMs to impart greater biological damage[9]. In humans, HMs can,

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over time, lead to accelerated aging, pre-disease states, and disease states[10]. However, human studies investigating the effects of low-to-moderate chronic HM exposures are limited.

This review highlights the possible contribution of hidden environmental HMs as potential disease triggers or strong disease contributors. We report the scientific data linking HM exposures to impaired pathways, common aging disorders, and/or impaired endocrine functions. In the first section, we describe general pathogenic effects of HMs; in the second section, we explain the known effects of lead, cadmium, mercury, arsenic, and nickel; in the third section, we describe the multiple HM effects, a pilot study on HM urinary levels and their interaction, and a hypothesis; in the fourth section we conclude. Our goal is to highlight the broad health effects of HMs and the intricacy of their possible interactions that may complicate future research studies. We further call for a necessary integrated multidisciplinary approach and a deep dive into this novel research field.

Heavy Metals' General Effects

Exposure to Heavy Metals

HMs are absorbed in plants and carried into vegetables, animal meat, and the human body[11]. Beyond *via* food intake, HMs can also be absorbed *via* inhalation, drinking water, showering, bathing, and skin contact.

Those HMs most commonly known to be toxic to humans are lead, cadmium, mercury, arsenic, and nickel, but the list is longer. Arsenic is included in this group because of its heavy-metal-like toxicity. HM blood levels reflect in greater part ongoing exposure. Once absorbed, HMs can be partially eliminated based on potential individual clearance abilities, but they cannot be degraded, and thus they may localize in organs (e.g., liver, heart, kidney, brain, soft tissue)[12]. Once HMs accumulate in the body, they cause harmful effects; however, we lack human studies examining the synergistic action of HMs; their correlation with broad biological, biochemical, and clinical parameters; and human genomic predisposition to increased toxicity. Furthermore, the potential toxic effects of HMs are often misrepresented by established HM safety levels[8].

Mechanisms of Actions

Once absorbed, HMs induce oxidative stress, a factor common to inflammatory diseases, and interfere with cellular redox regulation, thereby causing oxidative injury on DNA, lipids, and proteins, and/or activating signaling cascades contributing to cell proliferation. They also inactivate tumor suppressor genes and inhibit DNA repair systems, thus contributing to genomic instability and mutations. Most HMs are highly reactive and form complexes with other compounds (e.g., oxygen, sulfide, chloride), thereby eliciting toxic effects. HM compounds have unique mechanisms; for instance, cadmium interrupts cell-cell adhesion, and vanadate interacts with protein phosphatases' binding sites[13]. HMs can impair microRNA expression, markedly in the brain[14].

Moreover, HMs can disrupt various key cellular functions and determine functional and essential mineral impairments at the tissue and cellular level[13]. Essential minerals are metals which in trace amounts are essential to physiological processes; for instance, iron is key in oxygen transport and zinc in metabolism; manganese and selenium are pivotal in antioxidant defense. However, these essential minerals become harmful at too low or high concentrations. The essential mineral concentration influences antioxidant enzymes activity; a small essential-mineral-level change impairs enzymes metabolism, leading to diseases[15].

These key essential mineral concentrations may be disrupted by the accumulation of HMs, for which there are no beneficial concentrations[16]. HMs interact and compete with micronutrients or essential minerals for absorption, transport, binding to proteins and enzymes, metabolism, sequestration, and excretion. They can also disrupt pathways and have toxic oxidative effects. HMs may substitute for the essential minerals' functions; for example, lead can substitute for calcium, cadmium can replace zinc, and aluminum can substitute for many trace elements. HMs compete with nutrient binding sites on receptors, metallo-enzymes, and proteins. Further, accumulated and stored HMs impair metabolic functions, hormones, and enzymatic action; create pro-oxidant and antioxidant imbalance; and disrupt glutathione metabolism. The essential minerals iron, copper, chromium, cobalt, and vanadium at high concentrations, and the HMs cadmium, arsenic, and nickel mediate the formation of free radicals[17,18].

Mercury, cadmium, and other HMs inactivate several enzymatic reactions, amino acids, and sulfur-containing antioxidants, as they have high affinity for sulfhydryl groups (e.g., as in

N-acetylcysteine and glutathione), thereby reducing oxidant defense and increasing oxidation. Mercury and cadmium, for example, bind to metallothionein and substitute for zinc, copper, and other trace metals, impairing the metallo-enzymes' effectiveness[18]. Neurotransmitter synthesis and action are also impaired by HM toxicity[19]. Accumulated HMs can cause various disorders, including cancer, kidney dysfunction, infection, and endocrine derangements[10,20-23]. Lead, cadmium, mercury, and arsenic rank among the top toxic HMs of public health significance. They are systemic toxicants known to induce damage in multiple organs, even at lower levels of exposure, and are classified as human carcinogens (known or probable) by the Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC)[24].

Brain Effects

HMs can cause neurological effects as they induce brain toxicity by passing the blood-brain barrier and trigger damage by inducing free radicals within cells and mitochondria, thereby leading to the oxidation of macromolecules, including lipids, proteins, and DNA. The resultant oxidative and nitrosative stress causes apoptosis and/or necrosis of neurons and glia, compromising motor, sensory, cognitive, and psychological functions[12,19,25-33].

Lead, cadmium, mercury, arsenic, nickel, aluminum, gold, titanium, and thallium are recognized neurotoxins. Increased exposure to any of these HMs may play a role in the increasing prevalence of autism, Alzheimer's disease (AD), attention deficit hyperactivity disorder, and other neurological disorders[25-27]. While physiological body functions require essential minerals, some are also neurotoxicants at abnormal doses, for instance, manganese and selenium; selenium in particular has a narrow beneficial range of safe-dose levels, above which is neurotoxic[26]. Further, AD may be triggered by essential ions derangements, leading to critical biological impairments and events contributing to neurodegeneration and cell death. Although the causes of neurodegeneration are multifactorial, evidence indicates that changes in the balance of redox transition minerals, especially iron, copper, and other trace minerals, are contributing factors and that their levels in the brain are elevated in AD. Further, aluminum was found in higher concentrations in the brains of AD patients[34-36], nonetheless aluminum's suggested minimum-risk level (MRL) is still very uncertain; the US Mayo Clinic suggests a value of <6 ng/L[37]. Copper, zinc, aluminum, and manganese are also involved in other neurodegenerative disorders[38].

Vascular Effects

HMs have several vascular effects: nitric oxide (NO) inactivation, endothelial dysfunction, vascular smooth muscle dysfunction and degeneration, inflammation, concentration-dependent cell proliferation/death, oxidation, reduced antioxidant defense, immune and mitochondrial dysfunction, atherosclerosis, coagulation, and thrombosis, decreased serum HDL, increased serum total cholesterol/LDL/non-HDL cholesterol/triglycerides/C-reactive protein (CRP), and vasoconstrictive prostaglandins. HMs also cause electrocardiographic alterations, catecholamine arrhythmogenicity and arrhythmias, myocardium degeneration/fibrosis, and myocarditis[18,39-48]. Mercury, cadmium, and other HMs inactivate catechol-O-methyltransferase, increasing epinephrine, norepinephrine, and dopamine, which lead to elevated blood pressure[18,49].

Clinically, these effects contribute to HTN, coronary artery disease (CAD), myocardial infarction, and cardiovascular events[18]. Further, a recent cohort study[50] reported that serum levels of lead, mercury, and cadmium are associated with CAD in the elderly. Thus, HM toxicity, and in particular lead, mercury, and cadmium exposure, should be ruled out in subjects with HTN and cardiovascular disease (CVD)[18].

Immune System and Inflammation

HMs can increase allergic reactions[51], and have antibiotic effects (e.g., arsenic use in the animal meat industry), thereby killing beneficial microflora[52]. In mice, evidence suggests cadmium induces immunosuppression by activating corticosteroids, such as corticosterone[53]. Increased generation of hydrogen peroxide and superoxide anion, depletion of protein-sulfhydryl contents, and lipid peroxidation are induced by nickel-carbonate hydroxide playing an important role in nickel carbonate hydroxide-induced lymphocyte death *in vitro*[54]. In a study[55], when rats were exposed to different levels of nickel sulfate, T and B cells lymphocyte subpopulations were stimulated at lower doses and suppressed at the highest doses. In humans, mercury exposure is linked to inflammation markers and autoimmu-

nity[56]. We know that mercury exposure reduces humoral response, increasing susceptibility to acute and even chronic infections, which may reduce long-term survival[20]. Infections stimulate inflammatory markers and leukocyte count, which may indicate the degree of aging, predict elderly long-term survival, and better prognosticate total and cardiovascular mortality compared to total cholesterol or low-density lipoproteins[57]. If low-chronic HM exposure constantly excessively stimulates inflammatory systemic markers, deleterious effects, precocious aging, and increased mortality may result. HMs have been found to impair the bowel microflora, increase intestinal mucosa permeability[52], and thus lead to leaky gut syndrome. Impaired microbiota and leaky gut syndrome can further increase systemic inflammation. For instance, lipopolysaccharide (LPS), an endotoxin of Gram-negative bacteria, is particularly inflammatory because it triggers auto-amplificatory reactions after activating monocytes and macrophages, and further activates the inflammasome, which produces several cytokines, including interleukin-1β, and interleukin-18[58]. Thus, by altering the microbiome and the intestinal barrier permeability and increasing susceptibility to infections, HMs may contribute to the pathological LPS passing through the intestinal barrier, entering the circulation, and leading to a general inflammatory state.

Studies have reported how even diet components are modulating the absorption, retention, counteractive effects, and elimination of HMs in animals and humans[52,59].

Heavy Metals as Endocrine Disruptors

HMs can impair neuroendocrine and thyroid signaling, resulting in adverse effects on development, behavior, metabolism, reproduction, and other functions[21].

Of interest, HMs can act as endocrine disruptors, as they may cause impaired reproduction, subfertility, infertility, impaired hormone synthesis, menstrual cycle abnormalities, anovulation, and early reproductive senescence. In humans, HMs are inversely associated with blood concentrations of luteinizing-hormone (LH) and with mature oocytes and oocyte yield following ovarian stimulation. HMs are also associated with uterine fibroids. In mice, HMs decrease LH and the fluidity of the pituitary membrane and suppress LH frequency; they also increase follicle-stimulating hormone (FSH) release, decrease ovarian weight and follicle number, increase follicle atresia, and decrease uterus size; height of epithelial cells and endometrial glands; and myometrium thickness[60]. Several HMs (e.g., lead, cadmium, mercury, nickel) are defined as metallo-estrogens because they can mimic the effects of estrogen[61,62].

Specific Heavy Metals

Lead and Its Effects

Two main routes of lead exposure are contaminated food and water and inhalation of aerosols and dust particles containing lead. Lead exists in an organic and inorganic form. Organic lead is more toxic than inorganic lead, as it is better absorbed. Lead is absorbed at 5-10% from the gastrointestinal tract and at 50-70% from the lungs. Recently absorbed lead remains in the red blood cells with a half-life of 20-40 days; it is eliminated mainly *via* the kidney. In humans, the organ that absorbs the highest lead percentage is the kidney, followed by the liver, brain, and heart; the most vulnerable target for lead is the central nervous system, causing lack of attention, memory loss, and headache. However, most long-term absorbed lead is localized 90% in bones, with a half-life of 25-30 years[63]. EPA regulates that Maximum Contaminant Levels (MCLs) allowed for lead in drinking water are 15 μg/L. Through water, lead absorption is 35-50%, and more than 50% in children. The blood-lead level range in children from various countries in Europe is 1-19 μg/dL; however, it is understood that even 5 μg/dL in children below age 12 may affect neurobehavior; thus, to minimize lead-related hazards, trends are shifting to lower levels[64].

A HuffPost analysis[65] of lead-poisoning data of USA cities found an association between cities with high African-American percentages and elevated lead-poisoning rates. In the years 1999-2004, African-American children were 1.6 times more likely to have a positive blood-lead test than white children. The disparity was even stronger in the children with extremely high lead levels (≥10 μg/dL): African-American children were almost three times more likely than white children to have highly elevated blood-lead levels, which cause the most damaging health effects. According to the World Health Organization (WHO), child exposure to high lead levels can lead to nervous system damage, behavioral impairments,

and intellectual infirmities. Lower levels of lead exposure (<10 μg/dL) can also cause neurological damage, dyslexia, shortened attention span, attention deficit disorder, reproductive organ damage, and HTN. Lead may be responsible for increased risks for cancer, especially of the stomach[66-68]. Lead exposure is associated with meningioma risk in women[69]. For children, there is no safe exposure threshold, and infants, fetuses, and kids under 6 years old are the most sensitive to lead[65].

In homes, lead exposure comes from paint, but also from crystals, ceramics, cosmetics, and medicines. Once in the body, lead replaces calcium; interacts with proteins, interfering with their function (e.g., sulfhydryl enzymes); and competes for essential cations' binding sites of enzymes, inhibiting their function. In rats, lead exposure resulted in significant inhibition of delta-aminolevulinic acid dehydratase (ALA-D) activity and glutathione depletion in blood, with significant reduction of blood hemoglobin, red-blood cell levels, superoxide dismutase, and catalase activities; significant increase in blood and brain reactive oxygen species (ROS); and significant decrease of the glutathione reduced-oxidized ratio accompanied by a significant increase in blood- and brain-lead concentration[70]. Importantly, selenium protects from lead toxicity[71].

Lead binds to cellular membranes and triggers lipid oxidation by altering membrane physical properties and increasing lipid oxidation rates[72]; it induces oxidative damage to brain, heart, kidneys, and reproductive organs by affecting membranes, DNA, and antioxidant defense systems. Even if it is known that lead exposure causes several diseases, including cognitive impairment, neurodegenerative disease, kidney disease, and HTN, the relevance of oxidative stress in low-lead exposure-related diseases has been criticized, as most mechanistic studies were conducted at moderate-high lead levels[29].

Given lead inhibition of heme synthesis, exposure to high lead levels is associated with anemia; a GWAS study[73] of blood lead reported associations near the ALA dehydratase (ALA-D) gene, suggesting that genetic and environmental factors contribute to blood-lead levels.

Brain Effects

Lead is neurotoxic[26]. In lead-exposed cultured astrocytes, significant chaperone deficiency was evident, which could underlie protein conformational diseases (e.g., AD). Early-life lead exposure was implicated in subsequent amyloidogenesis occurring in rodents in old age[74]. Lead exposure is detrimental to the nervous system; however, environmental factors increase nervous system susceptibility to lead, and early-life exposures may cause neurodegeneration in later life[75]. In children with sickle cell anemia, cases have been reported of lead-induced foot and wrist drop, generalized weakness, and distal paralysis, associated with slow peripheral nerve conduction velocities. Chelation therapy resulted in a return of strength over several months[76].

Lead co-exposure, even at very low levels, further enhances manganese toxicity, which attacks the dopaminergic system. In fact, lifelong manganese exposure is significantly associated with changes in odor discrimination, motor coordination, cognitive abilities, and increased serum-PRL levels[77].

As lead accumulates in bone with a half-life of 25-30 years[63], researchers tested blood- and tibia-bone-lead levels together with cognitive function in lead-exposed and unexposed workers in 1982 and then again 22 years later[78]. In exposed workers, bone-lead level predicted reduced current cognitive function and cognitive decline over 22 years. In the lead-exposed workers ≥55 years old, higher bone-lead levels predicted poorer cognition. As no association was found between bone-lead level and recent exposure, cumulative lead-body burden most likely caused the cognitive decline[78]. In a study[79] in ex-lead workers, peak-tibia lead was between 2.2 and 98.7 μg lead/g of bone mineral. Compared to controls, ex-lead workers performed worse over time on three tests of visual ability, verbal memory, and learning. In ex-lead workers, peak tibia lead predicted decline of verbal memory and learning, visual memory, executive ability, and manual dexterity[79]. On average, an increase of 15.7 μg/g of peak-tibia lead corresponded to a decline of at least 5 years of age at baseline; thus, cognition can progressively decline due to past occupational lead exposures[79].

Another study[80] indicated that low-lead levels contributed to cognitive impairments in elderly men. Cognitive tests for memory, language, attention, perceptual speed, and spatial copying were performed, and men with higher blood-lead levels recognized fewer line-drawn objects, needed more time for the same precision on a perceptual comparison test, and remembered and defined fewer words, compared to men with the lowest blood-lead levels. Men with higher blood- and tibia-lead levels copied spatial figures less precisely; men with higher tibia-lead levels were

slower in memory responses[80]. In a cohort of 258 three-year-old Chinese children of Guiyu (recycling-waste-exposed group) and Nanao (control group), lead was negatively correlated with cognitive and language scores, while free triiodothyronine (FT_3), free thyroxine (FT_4), and TSH did not significantly mediate the association of lead with mental development of children. Cadmium did not correlate with cognitive or language scores. Thus, lead exposure reduced cognitive and language skills and affected thyroid function, but thyroid disruption was not implicated in the lead-cadmium co-exposure-induced neurotoxicity[81]. In a study[82] of 118 mothers, neural-connectivity pattern differed between lead-exposed and non-lead-exposed fetuses; the latter showed stronger age-related increases in cross-hemispheric connectivity, while the lead-exposed fetuses showed stronger age-related increases in posterior cingulate cortex to lateral prefrontal cortex connectivity in functional magnetic resonance. Childhood lead exposure is associated with lower socioeconomic status and cognitive function at 38 years old and with an IQ decline[83].

Of note, lead effects are expected to be more impactful during the development stages of children and adolescents, compared to adulthood. Childhood lead exposure can condition the neurodevelopment and psychologic characteristics; blood-lead levels at 6.5 years of age are inversely correlated with volumetric measures of brain structures implicated in emotional regulation and executive performance (e.g., gray and white matter of temporal, parietal, and frontal lobes). A study[84] investigated whether neuroanatomical differences in structural brain volumes were associated with childhood lead exposure at 78 months of age and found that females had gray and white matter volume loss in the right temporal lobe and reduced gray matter volume in the frontal lobe and males reduced white matter volumes in the frontal, temporal, and parietal lobes associated with increased blood-lead level at 78 months of age. Thus, lead-related effects are mediated differently between males and females. Early life lead exposure seems to cause in adulthood cognitive decline and psychiatric problems, such as specific phobia and anxiety[85].

A prospective cohort study[86] of 107 cases and 319 control subjects revealed a strong association between lead- and cadmium-blood levels and amyotrophic lateral sclerosis (ALS) risk (odds ratio [OR]=1,89 and 2,04, respectively), while zinc levels were linked with a reduced risk. A study[87] of the association between blood-lead concentrations, plasmatic biomarkers of bone synthesis [procollagen type 1 amino-terminal peptide (PINP)] and resorption (C-terminal telopeptides of type 1 collagen [CTX]) and ALS risk in 184 cases and 194 control subjects reported a 1.9-fold augmented ALS risk for a doubling of blood-lead concentrations and, interestingly, blood-lead association with CTX, but not PINP, among cases and control subjects. The role of lead exposure in Parkinson's disease (PD) onset was investigated in several studies[88,89], showing >2-fold increased PD risk for the highest lifetime exposure quartile compared with the lowest quartile[90], and an overall 50% augmented risk for PD[89].

Cardiovascular Effects

Acute lead exposure below the reference-blood concentration increases systolic blood pressure by augmenting angiotensin II levels *via* angiotensin-converting enzyme (ACE) activation. Thus, acute lead exposure triggers early mechanisms of HTN onset and is an environmental risk factor for CVD[91]. Additional mechanisms of lead-induced vasculopathy are NF-kB stimulation and inflammation with LDL oxidation and monocyte adhesion, sodium retention, increased adrenergic activity, endothelial injury, vascular remodeling, and platelet activation, contributing to HTN, atherosclerosis, CVD, and thrombosis[41].

A study[92] showed that low-chronic blood lead levels of 12 μg/dl below the WHO-established values increased rats' systolic blood pressure and vascular phenylephrine reactivity by increasing renin-angiotensin system activity and ROS production and by reducing NO bioavailability.

In humans with excessive lead exposure, postmortem evidence revealed morphological, biochemical, electrical, and mechanical myocardium impairments. Vascular degeneration, abnormal vascular smooth muscle function, and altered vessel compliance have been noted in humans with chronic or acute toxic lead exposures and confirmed in experimental animals. Lead-poisoning-related cardiovascular disturbances include augmented vascular reactivity to alpha-adrenergic agonists, increased catecholamine arrhythmogenicity, electrocardiographic alterations, impaired myocardial contraction to inotropic stimuli, structural biochemical degeneration of the myocardium, myocarditis, hypercholesterolemia, atherosclerosis, and HTN. Subclinical lead poisoning has less certain cardiovascular effects. However, low-chronic lead

exposure levels causes HTN in both animals and humans by multifactorial pathogenic effects: inactivation of endogenous NO, increased sympathetic activity and plasma norepinephrine, elevated renal beta-adrenergic receptor density, elevated plasma ACE activity and activation of the renin-angiotensin-aldosterone system, plasma renin activity (PRA), angiotensin II, and aldosterone levels, increased kininase I and kininase II activities, inhibition of vascular smooth muscle Na+-K+ ATPase, leading to increased intracellular Na+ and Ca2+[93], increased endothelin production, reduced vasodilatory prostaglandins, and elevated vasoconstrictive prostaglandins[40]. A study[94] in rats reported that lead exposure *in vivo* increased activity of one or more steps in the late pathway of aldosterone biosynthesis and that the hypertensive effect of lead implies relative hyperaldosteronism and may be more evident when aldosterone secretion is stimulated by ACTH.

In a study[95] of 50 occupationally lead-exposed and 50 non-exposed workers, the association of occupational lead-exposure with elevated blood pressure, serum aldosterone, and plasma renin activity was investigated. Blood lead and serum-aldosterone levels were significantly increased in occupationally lead-exposed males and females compared to control subjects. In the lead-exposed workers, plasma-renin activity was, respectively, significantly decreased and increased, compared to the control subjects. Thus, occupationally low lead levels appear to influence serum-aldosterone level and plasma-renin activity, with a gender-mediated effect on renin; and blood-lead was associated with blood-pressure-related hormones[95]. However, the study was of small size and should be replicated.

In clinical and experimental studies, chronic low-level lead exposure has been linked to HTN and other cardiovascular disturbances[96]. Thus, lead can induce significant changes in the cardiovascular system at the cardiac, vascular, and central nervous systems[96]. Low lead exposure induces HTN not due to lead-mediated toxic effects on the marrow, kidneys, or other organs. Lead's hypertensive effects manifest at blood concentrations of 10-40 μg/dl; however, some studies have not reported a significant correlation of blood-lead level with systolic and/or diastolic blood pressure[97]. This discrepancy may be due to the fact that lead-induced HTN derives mostly from past rather than current exposures; thus, blood pressure values should be related to bone and not blood-lead level[97]. The hypertensive effects of lead were confirmed in experimental models.

A study[50] reported that serum levels of lead were associated with CAD in the elderly. The evidence is sufficient to imply a causal relationship of lead exposure with HTN; it is suggestive but not sufficient to imply a causal relationship of lead exposure at blood lead levels <5 μg/dL with CVD, coronary heart disease, stroke mortality, and peripheral arterial disease. However, low-level lead exposure can be a cause of arterial stiffness[98]. There is also suggestive but insufficient evidence to imply a causal relationship of lead exposure with heart rate variability[99].

Lead-exposed workers showed anomalies of the heart conduction system, such as high QRS voltage, likely mediated by the ryanodine receptor 1, which regulates calcium efflux from the sarcoplasmic reticulum[100], QT-interval prolongation, and reduced heart rate[101]. In this regard, studies are warranted investigating whether low-chronic level cumulative lead exposure contributes to any heart-conduction abnormalities.

Among 14,289 US adults ≥20 years old participating in the Third National Health and Nutrition Examination Survey (NHANES-III) between 1988-1994 and followed up to 2011, blood-lead concentration increase from 1.0 μg/dL to 6.7 μg/d, representing respectively the 10th and 90th percentiles, was associated with all-cause mortality (hazard ratio [HR] 1.37, 95% confidence interval [CI] 1.17-1.60), CVD mortality (HR 1.70, 95% CI 1.30-2.22), and ischemic heart disease mortality (HR 2.08, 95% CI 1.52-2·.85). While the population attributable blood lead concentration for all-cause mortality was 18.0% (95% CI 10.9-26.1; 412,000 yearly deaths), the population attributable blood lead concentration for CVD mortality was 28.7% (15.5-39.5; 256,000 yearly deaths) and for ischemic heart disease mortality was 37.4% (23.4-48.6; 185,000 yearly deaths). Thus, low-level environmental lead exposure is a key risk factor for CVD mortality in the USA and has been overlooked[102]. Blood lead safety limits should be lowered, and screening criteria for lead exposure should be established in adults[99].

In African-American subjects, reduction in renal function was proportional to increased blood lead concentration[103]. Even low levels of environmental lead exposure (without the evidence of a threshold) may accelerate progressive renal insufficiency of nondiabetic patients with chronic kidney disease[104].

Endocrine-Metabolic Effects

Childhood lead exposure appeared to be a causative factor for hepatic steatosis and injury in young adulthood[105]. A study showed that high blood lead level at the beginning of lead exposure was proportional to the rate of increased fasting glycemia per year[106]. The long-term accumulation of lead has been associated with increased uric acid levels in middle-aged and elderly men[107]. Blood lead levels <25 μg/dL in adults, considered acceptable by current US standards, were associated with increased prevalence of gout and hyperuricemia[108].

A study[21] in 219 men reported blood lead level inversely associated with prolactin (PRL) and thyroid-stimulating hormone (TSH). A study in 5,628 Chinese adults reported a positive association of blood lead with elevated thyroid peroxidase antibodies (TPOAb) and TSH in women; no correlation was found in men. Thus, lead may induce thyroid autoimmunity in women[109].

A study in 4- to 8-year-old children indicated that seasonal blood lead increase may be due to higher serum-25-OH-vitamin D3 concentration in summer from higher sunlight-induced vitamin-D synthesis and probably higher intestinal lead absorption[110].

In men exposed to lead with a high lead body burden, increased parathyroid hormone (PTH) and 1,25-diOH-vitamin D3 were reported. Lead inhibits 1,25-diOH-vitamin-D3 activation of calcium channels and interferes with 1,25-diOH-vitamin-D3 regulation of calcium metabolism in osteoblastic bone cells[111].

In rats, long-term low- and high-level lead exposure caused osteopenia. Lead was incorporated in bone after 1 month of low (100 ppm) exposure with significant osteopenia after 12 months; high lead (5000 ppm) caused osteopenia at 3 months[112].

In a rat model of lead intoxication, bone lead was significantly increased, and serum calcium and ionized calcium were significantly decreased, as well as urinary cAMP excretion and circulating 1,25-diOH vitamin D3. Parathyroid and intestinal mucosa 1,25-diOH vitamin D3-specific binding was increased. Parathyroid weight was significantly increased according to secondary hyperparathyroidism probably due to hypocalcaemia and low 1,25-diOH vitamin-D3 levels[113].

In a study[114] of 126 Brazilian subjects between 50-82 years old, blood lead level was tested for association with salivary cortisol samples collected over two days at awakening, 30 minutes after waking, in the afternoon, and in the evening. Blood lead was positively associated with cortisol awakening response and overall cortisol concentration. Subjects with high blood lead levels showed higher cortisol at 30 minutes after awakening and in the afternoon than those with low blood lead levels. Blood lead was also positively associated with HDL and negatively associated with dehydroepiandrosterone sulfate (DHEA-S). Thus, lead exposure, even at levels below the reference-adult blood lead level recommended, may contribute in older adults to impaired cortisol pathway[114].

Reproduction

Lead is a metallo-estrogen, acting similarly to estrogens; in a human breast cancer cell line, lead activated the estrogen-receptor-1-α (ER-α) with the same potency of estrogen, stimulated cell proliferation, and induced expression of the estrogen-regulated gene progesterone receptor. The ability to stimulate the receptor was blocked by an antiestrogen[61].

Lead has been associated with male and female infertility. In men, lead was associated with reduced sperm count and decreased libido. In women, lead exposure was a risk factor for miscarriages and still birth[115]. It has also been reported that lead delays the timing of male puberty and negatively affects pubertal growth[116,117].

Blood lead level was reported significantly higher in azoospermic and oligospermic versus normospermic men; blood lead was inversely associated with sperm count[118]. In 941 male subjects, urinary lead was negatively correlated with sperm concentration, sperm count, progressive motility and sperm motility, decreased serum FSH, serum testosterone, and testosterone/LH ratio[119].

Lead was associated with delayed female growth and puberty[120] and with natural menopause in USA women, even after adjustment for bone turnover. Thus, lead exposure, even at low levels, may shorten women's reproductive lifespan[121].

After lead exposure, ovulatory function may be disturbed, with increased FSH. A nationally representative sample of USA women, 35-60 years old, with blood lead levels in the range of 0.2-17.0 μg/dL (mean of 1.6 μg/dL), showed that as the blood lead level rose, the serum-FSH levels increased in pre-menopausal women, post-menopausal women, and women with bilateral ovariectomy. Also, the LH levels rose as blood lead level increased in post-menopausal women and women with bilateral ovariectomy. For FSH, the

lowest blood lead level at which a relationship is detected is 0.9 μg/dL, and for LH, it is 3.2 μg/dL[122]. Another study[123] also found that blood-lead level and FSH correlate, and that 21% of the FSH variations can be explained by blood-lead levels.

In women of reproductive age, lead was associated with decreased LH, and decreased mature oocytes and oocyte yield following ovarian stimulation[60].

In rats, lead exposure decreases pituitary membrane fluidity, which can impair secretion and receptor binding but does not change the level of FSH, LH, and dopamine[124,125].

In human *in vitro* fertilization (IVF) studies[126] in women residing in the area of Taranto (Italy), an area influenced since 1986 by industrial activities and waste treatments, lead in the oocyte follicular fluid was associated with a significantly lower number of oocytes retrieval, compared to the control group.

In another study, lead was detected in 15% (5/33) of women with unexplained infertility and 3% (1/32) of fertile women[127]. Other studies[128] reported negative association of lead with infertility. Of note, lead urinary levels were also associated with uterine fibroids[129].

A study[130] of 114 women not occupationally exposed to lead reported lead concentration of 0.7 mcmol/L in maternal blood, 0.55 mcmol/L in umbilical cord blood, and 0.23 mcmol/L in breast milk, indicating that lead freely crosses the placental barrier from mother to fetus.

Another study[131] showed that blood-lead levels were higher (37.68 μg/dL) in women with preeclampsia compared to women without it (14.5 μg/L). A meta-analysis confirmed that blood lead levels are significantly associated with preeclampsia, with an increase of 1 μg/dL associated with a 1.6% increased likelihood of preeclampsia. Thus, lead is shown to be the strongest known risk factor for preeclampsia[132].

Lead exposure during gestation can lead to low birth weight (LBW), premature birth, and fetal bone growth impairment[112]. Blood lead has been associated with spontaneous abortions[133]. However, another study[134] did not detect association of blood lead level with adverse pregnancy outcomes. A USA study reported that even very low levels of maternal lead exposure may adversely affect preterm birth among males[135]. A study[136] in Mexico City detected a preterm birth rate almost three times higher in primiparous women with umbilical cord blood lead levels ≥5.1 μg/dL compared to primiparous women with umbilical cord blood lead levels <5.1 μg/dL, after adjustment for other risk factors for preterm birth. However, this difference was not detected in multiparous women.

Cadmium and Its Effects

Cadmium is in fertilizers, water, and cigarettes. Cadmium is absorbed *via* the gastrointestinal tract and lungs; once absorbed, it reaches the enteral-hepatic circuit and accumulates in liver and kidney. It is eliminated *via* the kidney and has a half-life of 16-33 years. While the blood concentration reflects acute exposure, the kidney tissue concentration reflects prolonged exposure. EPA regulations dictate that cadmium MCLs in drinking water should be 5 μg/L.

Cells exposed to cadmium have reduced antioxidant abilities likely due to the interaction of cadmium with zinc, iron, copper, and selenium causing a decrease in the antioxidant proteins glutathione peroxidase, superoxide dismutase, and catalase[137]. Cadmium depletes glutathione and protein-bound sulfhydryl groups, thereby enhancing ROS production (e.g., superoxide ion, hydroxyl radicals, and hydrogen peroxide)[138]. Per EPA and IARC, cadmium is a human carcinogen[24] and contributes to stomach, pancreatic prostate lung, and renal cancer[66,139-143].

Brain Effects

Chronic cadmium exposure can affect adult brain function, behavior, and learning ability[30], cause neurotoxicity[27] and peripheral polyneuropathy[144], and is implicated in AD[31] and sporadic motor neuron disease[145]. In rats, cadmium increased blood-brain barrier permeability and decreased microvessel antioxidant defense, potentially leading to brain microvascular damage[146]. In humans, prenatal cadmium exposure can impair cognitive development of offspring[147] and was correlated with slowed growth measured at 4 years of age[148]. In the NHANES III cohort of 5,572 subjects, urinary cadmium was associated with worse neurocognitive performance[149]. Further, in the NHANES cohort of 2,068 adults ≥60 years old, cognitive impairment, a possible prelude of AD, was shown to be linked to cadmium levels[150]. Similarly, this correlation was reported in Chinese subjects ≥65 years old[151].

Cardiovascular Effects

Cadmium inactivates catechol-O-methyltransferase, thereby increasing catecholamines, lead-

ing to elevated blood pressure[18]. Furthermore, it increases aldosterone synthesis[152] and decreases urinary sodium excretion before the onset of increased blood pressure[153]. Serum levels of cadmium in the elderly were associated with CAD[50]. Cadmium can mediate smoking-related damages in the cardiovascular system[154]. Cadmium exposure should be ruled out in subjects with HTN and CVD[18]. Cadmium appears to be one of the most significant contributing factors to cardiovascular events as well as to all-cause, cardiovascular-related, and cancer-related mortality when present in metal mixtures[155,156]. A Korean population-based, cross-sectional study[157] showed a strong correlation of blood cadmium with stroke and HTN, but not with ischemic heart disease. Data from the NHANES 2007-2010 reported urinary cadmium associated with vascular disease-related markers, such as LDL cholesterol, non-HDL cholesterol, triglycerides, and C-reactive protein[42].

Low levels of cadmium-body burden cause renal tubular damage, tubular necrosis[158], proteinuria, and renal dysfunction[159]. A study[160] on Chinese T2D-subjects reported that patients with high metallothionein antibody (MT-Ab) levels were more prone to cadmium-induced tubular damage. Renal cadmium reduces peroxisome proliferator-activated receptors (PPARs), which may lead to glucose intolerance, dyslipidemia, sodium retention, HTN, and zinc deficiency[18]. In 12,577 subjects of NHANES 2007-2012, blood cadmium worsened, mainly in females, glomerular filtration, and albumin excretion impaired by diabetes or HTN[161].

Endocrine-Metabolic Effects

Cadmium exposure is associated with liver necro-inflammation, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and liver-related and liver-cancer mortality[162].

The NHANES III studying 8,722 USA citizens over age 40 reported a significant association between urinary cadmium level elevations and fasting glycemia increase (110-126 mg/dl) as well as the number of subjects diagnosed with T2D[163]. In a Chinese cohort of 305 cases, urinary cadmium levels correlated with risk for gestational diabetes[164]. A longitudinal prospective study of 3,521 Chinese adults showed, during a three-year follow-up, increasing fasting glycemia in subjects with the highest urinary cadmium levels[165].

Animal studies[166] have indicated that cadmium exacerbates diabetic nephropathy. Cadmium also elevated fasting glycemia in an animal model of subchronic cadmium exposure before overt renal dysfunction was evident[166]. Cadmium could alter blood glucose levels by several cellular and physiological mechanisms; it could affect glucose metabolism by acting on various organs, including the pancreas, liver, adipose tissue, and the adrenal gland. Cadmium has direct cytotoxic effects on the islets of Langerhans, impairs insulin release, reduces insulinemia; and causes significant glycemia increase prior to overt renal dysfunction[166]. Thus, cadmium may contribute to some T2D forms and cadmium and diabetes-related hyperglycemia may synergistically cause kidney damage[166].

Researchers reported that in non-fasted rats, 30 minutes after acute exposure to a single cadmium dose (0.84 mg/kg, i.p.), plasma glucose levels became significantly elevated[167]. In a study[168] of subchronic cadmium exposure, rats given daily doses of cadmium (1.0 mg/kg) orally for 45 days exhibited significantly elevated fasting glycemia. Other authors[169] reported that cadmium significantly decreased cell viability in pancreatic β-cell-derived RIN-m5F cells, increased intracellular ROS generation, and induced mitochondrial dysfunction. The cadmium-induced events were reversed by pretreatment with the antioxidant *N*-acetylcysteine. Furthermore, cadmium induced pancreatic β-cell death *via* oxidative stress, downstream-mediated c-jun N-terminal kinases activation, and mitochondria-regulated apoptotic pathway[169]. Studies[170] showed that in pancreatic islets isolated from obese-hyperglycemic mice, cadmium was rapidly taken up in pancreatic tissue; while low cadmium levels (5 μM) enhanced glucose-stimulated insulin release, high cadmium levels (20 μM) significantly diminished insulin release. In rats, subchronic cadmium exposure increased the activity of all four enzymes responsible for gluconeogenesis in the liver and in the kidney[171].

Of note, administration of selenium concurrent with cadmium prevented the cadmium-induced hepatic gluconeogenic-enzymes increase and improved the cadmium-induced hypoinsulinemia, hyperglycemia, glucose intolerance, and the suppression of pancreatic secretory activity[172]. In isolated rat adipocytes, cadmium induced glucose metabolism and lipogenesis, and mimicked insulin effects[173]. Furthermore, cultured adipocytes isolated from previously cadmium-exposed rats decreased expression of the glucose transporter (GLUT4) and reduced glucose transport activity[174]. Cadmium-enhancing catecholamines

released from the adrenal gland may also increase glycemia[175]. In mouse renal cortical cells *in vitro*, cadmium concentrations not causing cell death decreased glucose uptake and expression of the sodium-dependent glucose transporter, SGLT1[176].

Cadmium levels, more than blood lead levels, were associated with hyperuricemia in men, especially non-smokers[177]. In non-smokers, increasing urinary cadmium levels were associated with increasing risk of osteopenia and osteoporosis[178]; CTX appears to be a reliable marker of cadmium-dependent bone loss[179]. In humans, prenatal cadmium exposure was correlated with slowed growth measured at 4 years of age[148]. Even relatively low cadmium exposure through diet and smoking increased the risk of low bone mineral density and osteoporosis-related fractures in elderly men[180].

Cadmium is also an endocrine disruptor. A study[181] reported a significant association of urinary cadmium with testosterone excretions in men, and with cortisol excretions and some mineralocorticoid metabolites in both genders; cadmium had an independent effect on the synthesis of sex hormones and corticosteroids. Thus, low-dose cadmium exposure stimulates steroid synthesis, which may explain the association of cadmium with steroid-sensitive cancers or metabolic disorders[181].

Cadmium can cause detrimental effects on the reproductive tissues. In males, serum testosterone and LH levels were significantly higher in a cadmium-exposed group than in the unexposed group, thereby highlighting the possible role of cadmium in increasing hormonal pituitary production[182].

A study[109] in 5,628 Chinese adults reported in women a positive association of blood cadmium to thyroglobulin antibodies (TGAb), hypothyroid status, and TGAb tertiles. In men, no correlation was found. Thus, cadmium induced thyroid autoimmunity in women. Nevertheless, another cross-sectional study[183] found an association between urinary cadmium and hypothyroidism in men, but not in women.

In a study[21] of 219 men, blood-cadmium was inversely associated with serum PRL, a marker of dopaminergic function, but not with TSH levels.

We already mentioned that cadmium replaces zinc. A study[184] investigating the zinc-deficiency effects on thyroid and PRL reported thyrotropin-releasing hormone (TRH) synthesized in the hypothalamus regulated the hypothalamus-pituitary-thyroid axis function, thus the TSH release from the anterior pituitary, and thyroid hormones serum concentration. TRH also enhanced PRL production. Pyroglutamyl aminopeptidase II (PPII), a zinc-dependent metallo-peptidase located in the anterior pituitary and medial basal hypothalamus degrades TRH and regulates TRH-induced TSH release from the anterior pituitary. Zinc-deficient male rats showed decreased pituitary and medial basal hypothalamic PPII activity and high TSH and PRL serum concentration. Zinc-replenished rats had normalized PPII activity and serum-TSH concentration. Thus, a long-term zinc-deficient diet down-regulated PPII activity independently of the thyroid hormone 3, the feedback mediator on TRH production, thus increasing TSH serum concentration and resembling subclinical hypothyroidism[184].

HMs and metalloids present in volcanic areas may lead to increased thyroid cancer incidence[185,186]. In the volcanic area of Mount Etna in Italy, boron, cadmium, and molybdenum are increased; rats prone to develop thyroid tumors by low-iodine diet and methimazole received *ad libitum* drinking water with boron, cadmium, and molybdenum at the same concentrations of the volcanic area residents' urine. The rat thyroid at 5 and 10 months had significantly increased histological transformation in follicular thyroid cells and reduced thyroid iodine content; thus, slightly increased boron, cadmium, and molybdenum concentrations accelerated thyroid transformation in hypothyroid rats[187].

Reproduction

Cadmium is a metallo-estrogen as it mimics estrogen effects *in vivo* in the uterus, mammary gland, and breast cancer cells, and forms a high-affinity complex with the estrogen receptor binding domain[62]. As low-dose cadmium has xeno-estrogenic activity (and at high concentration is cytotoxic) in different hormone-dependent tumor cell lines, a study[62] investigated whether low doses of cadmium administered *in vivo via* drinking water showed xeno-estrogenic effects in the anterior pituitary and uterus of ovariectomized rats. Cadmium [1 part per million (ppm)] and arsenic (0.1 ppm) increased the anterior pituitary and uterus wet weight; induced proestrus- and estrus-like vaginal smears; stimulated pituitary, uterine, and vaginal cell proliferation; and increased the expression of proliferation markers and soluble guanylyl cyclase α1 subunit, which is linked to hormone-dependent tumor progression[62]. Cadmium modified full-length es-

trogen-receptor-α protein levels. Cadmium exposure strongly reduced LH synthesis and release. Cadmium increased PRL synthesis. Thus, cadmium exerts at low doses strong xeno-estrogenic effects on the anterior pituitary[62]. In addition, testes are a target organ for cadmium; zinc transporters likely mediate the testicular uptake of cadmium *via* a mechanism of ionic mimicry[188]. The process of molecular ionic mimicry is probably acting for several HMs, which do not have specific transporters as they do not have any beneficial function *in vivo*. Vitamin C and vitamin E counteracted cadmium oxidative effects in rat testes[189]. Cadmium affected spermatozoa motility and counts; in rats, at high cadmium doses, the testis germinal epithelium was irreversibly impaired in a short time, producing toxic effects on spermatogenesis: spermatozoa count, and daily spermatozoa production were significantly reduced, and no motile sperm was identified. Medium cadmium dose reduced spermatozoa motility significantly[190]. However, testis injury occurred even at low-exposure levels. In the testis, cadmium caused structural vasculature and blood-testis barrier damage, cytotoxicity on Sertoli and Leydig cells, inflammation, oxidative stress by ionic mimicry and interference, interference with signaling pathways, epigenetic regulation of genes implicated in reproductive function regulation, apoptosis, necrosis at higher cadmium dosage exposures, and hypothalamus-pituitary-gonadal axis (HPG) impairment. Experimental animal studies[191,192] offered evidence of cadmium reproductive toxicity; however, human observational studies are controversial, likely due to study design and exposure heterogeneity, as well as additional pollutants' co-exposure.

Blood plasma cadmium levels were significantly higher in azoospermic and oligospermic versus normospermic men. Blood and seminal cadmium levels were significantly inversely associated with sperm count, motility, and morphology[118].

Of interest, ovarian cadmium concentration increased with age and was associated with oocyte development failure and ovulation failure. Also, ovulation could become ineffective due to failure of pick-up of the oocyte by the tubal cilia due to impairment of the oocyte-cumulus complex and cell adhesion molecules[192]. Cadmium is incorporated into the chromatin of the developing gamete[192].

Of interest, combined exposure of cadmium and insulin resistance caused subfertility. In a study[193], the *in vitro* effects of cadmium on human granulosa cells with insulin resistance were tested. Isolated human granulosa cells with insulin resistance from polycystic ovarian syndrome (PCOS) follicular fluid samples were incubated with or without 32 μM cadmium alongside control subjects' cells. The combined effect of insulin resistance with 32 μM cadmium in granulosa cells demonstrated a significant decrease of key enzymes and receptors' expression (e.g., steroidogenic acute regulatory protein, cytochrome-P450-family-11 subfamily-A-member 1, cytochrome-P450-family-19 subfamily-A-member-1, hydroxysteroid-17-beta dehydrogenase 12, 3-beta-hydroxy-steroid dehydrogenase, FSH-receptor, LH-receptor), progesterone, and estradiol compared to the control group's cells. Other molecular markers indicated apoptosis; the increased cell death leads to decreased steroidogenesis, which causes abnormal follicle development compromising fertility at the preconception stage[193].

Cadmium may contribute to unexplained infertility[127]. A study[127] investigated the role of heavy-metal endometrial concentrations in unexplained infertility. Endometrial biopsies were performed during cycle days 20-24 of the implantation window of 33 women with unexplained infertility and 32 fertile women[127]. Cadmium was found in 91% (30/33) of women with unexplained infertility and in only 34% (11/32) of fertile women, and the difference in endometrial-cadmium concentration was significant: 19.58 (range 1.46-30.23) μg/L in unfertile women and 0.00 (range 0.00-0.40) μg/L in fertile women[127].

In the Boston Birth Cohort of 1,274 women, preeclampsia risk was amplified by higher cadmium blood levels, while there was no associated risk with lead or mercury blood levels[194]; this was contrary to a meta-analysis reporting lead as the strongest risk factor for preeclampsia[132].

In the evaluation of birth outcome measures and heavy-metal exposure among a Saudi Arabian population, cadmium, which passes only partially through the placenta, had the strongest influence on birth outcome. Cadmium in the umbilical cord blood significantly influenced the crown-heel length, the Apgar 5-minute score, the birth weight, and the small-for-gestational-age measure. Also, higher maternal blood cadmium levels were associated with significant decreases in crown-heel length and placental thickness. As placental cadmium increased, cord length significantly increased and placental thickness significantly decreased[195].

Cadmium can also cause detrimental effects on the developing embryo[192]. It may impair trophoblast growth, cause placental necrosis, suppress steroid biosynthesis, and alter placental nutrient minerals handling, thereby contributing to implantation delay and possible early pregnancy loss[192]. A study showed cadmium accumulated in embryos from the four-cell stage onwards, and higher exposure dose inhibited blastocyst formation and caused blastocyst degeneration[192]. After implantation, oral or parenteral cadmium in animals caused several abnormalities in the embryo, depending on the dose and stage at exposure time[192].

Mercury and Its Effects

Organic mercury from the environment, including air, water, soil, and amalgam fillings, ethyl-mercury from old vaccines, and methyl mercury from seafood, is a toxin detrimentally affecting fetuses, newborns, infants, and adults. Of the methyl mercury ingested, 85% is absorbed by the gastrointestinal tract, 5% by the blood, and 10% by the brain. The main excretory routes are urine and feces; the mercury body half-life is *circa* 70 days. Methyl-mercury is highly present in seafood, and has been found at lower levels in eggs, meat, poultry, dairy, pasta, and vegetables. Mercury ingested *via* contaminated seafood is able to disrupt gastrointestinal digestion by inhibiting chymotrypsin, trypsin, pepsin, dipeptidyl-peptidase IV, and xanthine oxidase[137].

Ethyl-mercury from thimerosal in vaccines becomes about one-third inorganic and two-thirds organic, and the brain half-life organic fraction is about 14 days, while the total mercury half-life is 24 days; methyl-mercury mainly remains as such and has a brain half-life of about 60 days[196,197]. Inorganic mercury of the amalgam fillings is methylated to methyl-mercury by sulfate-reducing bacteria in the mouth. Amalgam fillings release even more mercury if exposed to electromagnetic frequency (e.g., mobile phones, cordless phones, Wi-Fi routers, and television)[198-200].

Of note, mercury has no beneficial function in humans and is the most toxic HM.

Mercury was shown to disrupt the expression of the metallothionein gene, impairing the synthesis of zinc-dependent metallothionein that is necessary for elimination of HMs, thus also impairing the clearance of other HMs[137].

Inorganic mercury is nephrotoxic, and methyl-mercury is neurotoxic. The lipid-rich brain is a favorite site for mercury, which binds to structural proteins and induces biochemical damages[26,201]. The methyl- and ethyl-group of mercury increases its hydrophobic ability to diffuse into the brain barrier and placenta. Methyl-mercury is absorbed *via* placenta and breast milk, and crosses the brain barrier. A quantity of methyl-mercury is de-methylated by the intestinal microflora and eliminated as inorganic mercury. Mercury induces oxidation and mitochondrial dysfunction, triggers displacement of iron, copper, and other trace minerals, reduces adenosine 5-triphosphate (ATP), and causes lipid peroxidation, increasing oxidative stress[18,202]. Mercury binds to sulfhydril groups of erythrocytes, proteins, metallothioneins, and antioxidants (e.g., N-acetylcysteine, alpha-lipoic acid, and glutathione). Mercury reduces the antioxidant enzymes, including glutathione[199], which alone provides 30-40% antioxidant plasma activity and protects the cell and mitochondria from oxidation, inflammation, and CVD more potently than other compounds. Mercury competes with the essential mineral selenium, a key component of the proteins regulating the intracellular redox system[203]. Studies[203] have shown that mercury has a higher affinity for selenium-containing groups by several orders of magnitude compared to thiol groups, allowing for multiple types of binding. We now know that the primary cellular targets of mercury are the seleno-proteins of the thioredoxin system (thioredoxin reductase 1 and 2) and the glutathione-glutaredoxin system (glutathione peroxidase). Mercury binds to the selenium site of these proteins and inhibits their function, thereby disrupting the intracellular redox system. Impairment of the thioredoxin and glutaredoxin systems leads to increase of intracellular ROS and consequently to glutamate exocytosis, calcium dyshomeostasis, mitochondrial injury and/or loss, lipid peroxidation, impairment of protein repair, and apoptosis. Methyl-mercury more potently inhibits the thioredoxin system, partially explaining its increased neurotoxicity. Mercury competes with selenium in metallo-enzymes, reducing their activity. Mercury-selenium complexes reduce selenium availability for glutathione peroxidase, which breaks down hydrogen peroxide and other toxic products. Other possibly important, identified, mercury-target seleno-proteins are P, K, and T. Also, the high selenium affinity of mercury subsequently depletes the selenium stores needed for the regeneration of seleno-proteins. This

mercury-induced selenium-deficiency inhibits seleno-protein regeneration, essential in cellular redox system restoration[203]. Selenium protects from mercury intoxication[71], but the protection depends also on the mercury form and may include: demethylating organic mercury into inorganic mercury, redistributing mercury to less sensitive organs, binding inorganic mercury and forming an inert mercury-selenium complex, reducing mercury absorption from the gastrointestinal tract, replenishing selenium stores, and reestablishing seleno-protein-intracellular redox activity[203]. It has been noted that an increase in plasmatic selenium in a cohort with high fish intake and thus high methyl-mercury levels may be associated with an increase in seleno-protein P, indicating an augmented demand in various organs for one or more seleno-proteins, among which seleno-protein P supplies selenium[204].

Low levels of mercuric compounds were shown to be toxic to human lymphocytes and monocytes and to decrease T-cell function[205]. The induction of T-cell apoptosis by mercuric compounds was mediated by the depletion of the thiol reserve, thereby predisposing cells to ROS damage and activating death-signaling pathways[202]. Mercuric compounds inhibited human monocyte function, induced apoptosis, and promoted ROS formation, mitochondrial membrane permeability, and loss of reductive reserve[206].

Chronic mercury exposure even at low concentrations causes cardiovascular, reproductive, and developmental toxicity as well as neurotoxicity, nephrotoxicity, immunotoxicity, and carcinogenicity. EPA and IARC have classified mercury as a human carcinogen[24]; mercury is a promoter carcinogen and contributes to stomach cancer[66,207].

It is worth considering that organisms very likely may respond differently to toxins based on their genetic predisposition[208]. In fact, recent eco-genetic-based studies have initiated to document genetic and epigenetic factors that may influence the toxicokinetics or toxicodynamics of mercury by mainly focusing on specific known pathways relevant to mercury detoxification and environmental responsive genes[209].

Brain Effects

The complex of cysteine and methyl-mercury resembles methionine, which is able to enter the brain, and thus it could lead to AD, Parkinson's disease, and, if absorbed by the placenta, autism[210-212]. Also, maternal hair exposure to mercury correlates to fetal brain mercury deposition[213]; thus, maternal metal exposure is a strong potential contributing factor to neurodevelopmental pathology. It is important to note that signs and symptoms of mercury exposure may appear after weeks or months of a latent period[137], which intuitively indicates difficulty in implicating mercury exposure with those symptoms and signs of toxicity.

EPA regulations mandate mercury MCLs of 2 μg/L in drinking water. However, EPA-established safety limits are not realistic in terms of the damage that low-level chronic mercury exposure can cause to the nervous system, thus likely contributing in children to neurodevelopmental problems and reduced IQ, as well as to cardiovascular and immune system impairments[201]. The main US recommended MRL-mercury value has been for some time 5.8 **μ**g/L, but other countries have modified it; Germany, for instance, has lowered it to 0.8[214], and two USA testing centers use values of 9.0 or 2.0 μg/L, representing an 11-fold range, and describing the uncertainties and variable safety risk assessments.

Documented mercury poisoning cases in adults indicate that the current MRL are failing[215]. Further, we have no measure available indicating that only slight neurological effects may be accumulating over time. Historically, documented examples of severe mercury toxicity are the Japanese Minamata Bay pollution and the "mad as a hatter" cases, the latter referring to mercury poisoning of hat-makers due to long-term mercury use in hat-making[216]. Mercury in the form of acute poisoning contributes to heart disease and nervous system damage (uncontrolled trembling, speech impairment, loss of motor control and sensory impairment, blindness, deafness, mental retardation, coma, and death)[217,218].

During prenatal life, mercury can impair neurodevelopment of offspring, especially affecting specific brain areas, such as the frontal and temporal lobes, corpus callosum, and hippocampus, increasing the risk of neural tube defects[219,220]. Even very low-level prenatal mercury exposure was associated with higher anxiety scores in children up to 8 years of age[221].

Cardiovascular Effects

A very recent meta-analysis revealed a J-shaped relationship between mercury concentration and various fatal and nonfatal cardiovascular outcomes, the turning points being at hair mercury levels of 1 μg/g for ischemic heart disease and 2 μg/g for stroke and all CVDs[222].

Mercury vascular effects include increased oxidative stress and inflammation, reduced oxidative defense, mitochondrial and immune dysfunction, endothelial and vascular smooth muscle dysfunction, thrombosis, dysregulation of prostaglandin synthesis[47], and hypercholesterolemia[43]. Notably, mercury could increase total and LDL-cholesterol also among adolescents[43]. Mercury toxicity can cause several clinical phenotypes, including coronary heart disease, myocardial infarction, HTN, cardiac arrhythmias, increased carotid intima-media thickness and carotid artery obstruction, cerebrovascular accidents, atherosclerosis, proteinuria, and renal dysfunction and insufficiency[39]. Mercury can have a long-term effect on the parasympathetic and autonomic nervous systems and reduce heart rate variability[199]. Furthermore, methylmercury appeared to induce an acquired "long QT syndrome"[223].

Of note, mercury inactivates catecholamine-o-methyltransferase, thereby increasing serum and urinary epinephrine, norepinephrine, and dopamine, which then increase blood pressure and may represent a clinical clue to mercury-induced toxicity. In fact, mercury intoxication can clinically and biochemically simulate pheochromocytoma[49]. Also, mercury poisoning can cause hyperreninemic hyperaldosteronism; however, it is unknown whether low levels of mercury can increase renin activity and aldosterone secretion[224]. Further, a recent study reported that serum-mercury levels were associated with CAD in the elderly[50]. In Eastern Finland, characterized by a low selenium-dietary intake, high intake of mercury from non-fatty freshwater fish was linked to increased risk of acute myocardial infarction, CAD, death from CVD, and any cause, all possibly due to lipid peroxidation triggered by mercury[225-227].

Thus, we suggest that mercury toxicity should be ruled out in HTN, CAD, cerebral vascular disease, cerebrovascular accidents, or other vascular diseases[39].

Endocrine-Metabolic Effects

Mercury level in red blood cells was correlated with prevalence of T2D[228]; mercury in a metal mixture was also a major contributing factor for gestational diabetes[229]. In children, a higher metabolic syndrome score was associated with higher maternal blood mercury concentration during pregnancy[230].

Mercury disrupts the thyroid function in vertebrates. A study[231] explored fish-muscle mercury concentration association with thyroid-related gene transcription, testing the hepatic expression of genes, including deiodinases (D1 and D2), transthyretin (TTR), and thyroid-hormone receptors (TRα and TRβ). Mercury levels were negatively correlated with D2, TTR, TRα and TRβ. Thus, in fish, mercury affects the regulation of genes key for thyroid function. These thyroid-related genes could be used as monitoring biomarkers for environmental thyroid hormone disrupting metals[231]. In 55 mercury-exposed individuals, a higher prevalence of elevated TSH and thyroid-echostructural alterations was present compared to 55 non-exposed subjects[232]. Mercury was associated with thyroglobulin autoantibody positivity[233].

A very recent cohort study[234] reported that intrauterine mercury exposure might contribute to increased risk of precocious puberty.

Reproduction

Mercury is a metallo-estrogen mimicking estrogenic action. In a human breast cancer cell line, mercury stimulated ER-α similarly to estrogen, cell proliferation, and expression of the estrogen-regulated gene progesterone receptor. The receptor stimulus can be blocked by an antiestrogen[61].

Hyperplastic endometrial tissue presented with a 4-fold higher mercury concentration than normal tissue. In human endometrial cell lines, mercury increased oxidative stress and altered the cytoskeleton. Thus, there is a link between mercury and endometrial hyperplasia[127]. Also, blood mercury levels are associated with uterine fibroids[129]. A study of 485 women in NHANES found mercury levels associated with lower LH[235], which was in turn accompanied by lower progesterone levels not sufficiently counteracting estrogens and thus allowing for endometrial hyperplasia and fibroids. In another study[60] of women following ovarian stimulation, mercury was associated with decreased LH, mature oocytes, and oocyte yield.

Also, mercury in hair is negatively correlated with oocyte yield and follicle number after ovarian stimulation[236], and women with mercury concentrations 1 ppm above the EPA references had lower oocyte yield[237]. Dermal exposure to creams containing high mercury levels caused accumulation of mercury in mouse ovaries[238].

A study[239] reported reduced fertility in dental workers exposed to mercury. Furthermore, mercury levels are negatively associated with

fecundity in the first pregnancy[240], and there are reports of negative association of mercury with fecundity, infertility, and fertilization rates in IVF[127,237].

In addition, term low birth weight was found more likely in women living in areas with increased total mercury in fish; and risks for term low birth weight or preterm birth were 10-18% more likely in African-American mothers residing in areas with the highest total fish mercury concentration[241]. A large community-based study comparing women with at-term deliveries with women with deliveries before 35 weeks of gestation reported that the latter were more likely to have hair mercury levels $\geq 90^{th}$ percentile[242].

Maternal hair total mercury levels were negatively associated with infantile weight and growth rate during twelve months after delivery, thus low-level prenatal mercury exposure may impair fetal and infant growth[243]. Another large study[244] indicated only a small increase in risk for small-for-gestational-age infants born to women exposed to mercury. However, a small study of an immigrant community in New York detected no association between maternal mercury exposure and low birth weight or preterm birth[245], likely due to the limited study cohort. Of note, the negative effects of prenatal mercury exposure on nutritional status, growth velocity, and neurodevelopment of infants were counteracted by maternal folate status[246,247].

Arsenic and Its Effects

Exposure to arsenic occurs *via* contaminated water, food, soil, and air[248]. Organic arsenic is less toxic than inorganic arsenic[52]; arsenic is eliminated *via* the kidney and its half-life is about 60 hours[249]. EPA regulations state arsenic MCLs in drinking water are 10 **μg**/L. With lead, mercury, and cadmium, arsenic is among the most important toxic HMs regarding public health significance. Arsenic mostly exists in a trivalent or pentavalent state or as calcium or sodium salt; sodium arsenite or arsenic trioxide react with sulfur groups of enzymes and inhibit them. In its pentavalent form, arsenic uncouples the mitochondrial oxidative phosphorylation. Most ingested inorganic arsenic is removed *via* the urine and the rest is transformed, causing molecular stress *via* various mechanisms, such as oxidative stress, chromosomal aberration, growth inhibition, apoptosis, and cellular morphological alterations due to cytoskeletal structural elements disruption[250]. In addition, arsenic toxicity may be characterized by DNA-methylation impairment, inhibition of DNA repair, and modulation of signal transduction pathways; these mechanisms may overlap and contribute to arsenic-induced carcinogenesis. Interactions of trivalent arsenicals with thiol groups of zinc-finger proteins play a role in arsenic carcinogenesis. However, inhibition of the DNA-repair mechanism is likely pivotal in arsenic carcinogenesis[251]. EPA and IARC classify arsenic as a human carcinogen[24]. Arsenic-related water drinking is mainly related to kidney, skin, and bladder cancer; arsenic also induces stomach, lung, liver, and uterus cancer, with the skin being perhaps the most sensitive site[66,252]. Populations outside the United States exposed to arsenic-contaminated drinking water showed cancer increases only at concentrations of several hundred **μ**g/L. USA populations exposed to drinking water with arsenic concentrations up to about 190 μg/L showed no increased cancer incidence[253].

Brain Effects

Beyond acute toxicity, arsenic is able to cause health disorders due to low-chronic exposure, including mental effects. Studies[26] conducted in areas particularly affected by arsenic exposure revealed that arsenic exposure was associated with various neurologic problems, can lead to mental retardation and developmental disabilities (e.g., physical, cognitive, psychological, sensory and speech impairments), and acts as a neurotoxicant. Studies in China and Bangladesh[33] reported that mental health problems (e.g., depression) were more common among subjects with arsenic exposures. A study[254] in Myanmar revealed that residents drinking water with low arsenic concentration presented, respectively, subjective and objective symptoms of peripheral neuropathy at arsenic water level of >10 parts per billion (ppb) and >50 ppb. Arsenic exposure in children can affect their cognitive development, speech, and visual perception, independent of lead-related effects[255,256], even in children with urinary arsenic below the safe declared concentration limit of 50 μg/L.

Cardiovascular Effects

Genetics, environment, and nutrition interact to contribute to the arsenic-related effects on blood pressure[257] and to the cardiovascular effects and disease[258,259]. Chronic arsenic poisoning is an independent risk factor for cardiovascular disorders,

chronic ingestion of arsenic contaminated water is associated in a dose-response manner with impaired microcirculation, prolonged QT interval, carotid atherosclerosis, HTN, CAD, and cerebral infarction. The detrimental cardiovascular effects of chronic arsenic exposure may be irreversible. High arsenic exposure causes major adverse cardiovascular effects[260]. The Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh, prospectively investigated the arsenic-health effects, predominantly at low-to-moderate exposure levels (0.1 to 864 μg/L, mean 99 μg/L), in more than 20,000 men and women, and found that low-to-moderate arsenic exposure had adverse effects on the risk of high blood pressure, neurological dysfunctions, premalignant skin lesions, and all-cause and chronic disease mortality[261]. A recent systematic review and meta-analysis confirmed that chronic exposure to very low concentration of arsenic (<10 μg/L) is correlated to CVD[262].

Environmentally relevant arsenic trioxide (arsenite) concentrations activated in endothelial cells the inflammatory transcription factor NF-kB, increased DNA synthesis, and induced oxidation and concentration-dependent cell proliferation or death[44]. In another study[45], arsenic induced endothelial dysfunction, including inflammatory and coagulating activity, and impaired NO balance.

A study[263] reported a higher odds ratio for chronic kidney disease in subjects with high urinary total arsenic levels.

Endocrine-Metabolic Effects

In a prospective study, among 1,694 diabetes-free subjects (45-75 years old) recruited in 1989-1991 and followed through 1998-1999, T2D manifested in 396 of them[264]. Their urine inorganic arsenic, monomethyl-arsenate, and dimethyl-arsenate were tested as biomarkers of arsenic metabolism. Lower monomethyl-arsenate was associated with higher T2D incidence; dimethyl-arsenate was associated with higher T2D incidence only when monomethyl-arsenate decreased, and urine inorganic arsenic was associated with higher T2D incidence also when monomethyl-arsenate decreased[264]. Also, arsenic was positively associated with HbA1c levels in T2D patients[265].

A review study[266] reported that there was limited-to-sufficient evidence for arsenic association with T2D in areas with ≥150 μg arsenic/L in drinking water and no sufficient evidence supporting arsenic association with T2D in areas with <150 μg arsenic/L in drinking water. However, more recent studies with improved outcome and exposure measures supported the association between arsenic and T2D[266]. In Pakistan, a study[267] reported an increasing T2D burden related to arsenic exposure. Arsenic pesticides increase glycogenolysis, gluconeogenesis, glycolysis, ROS, and oxidative stress; cause beta-cell dysfunction and insulin resistance; and decrease GLUT translocations, insulin-mediated glucose uptake, and insulin mRNA and secretion, thereby increasing glycemia. Further, prenatal arsenic exposure was linked to increased T2D rate in young adults[268].

Evidence suggests the oral-hypoglycemic pioglitazone's differentiating effects on adipose tissue *in vitro* (induction of adipogenesis by PPAR-γ activation) is inhibited by arsenic; thus, arsenic interferes with adipogenic signaling at or downstream of the level of PPAR-γ[269]. However, a study reported on the contrary that low-level arsenite (0.25 mcmol/L or 0.5 mcmol/L applied for 3 days) activated adipose-differentiation transcription genes, including PPAR-γ[270]. Experimental variations, time, and concentration may underlie the discrepancy of results. In addition, in adipocytes, trivalent arsenicals inhibited insulin-stimulated glucose uptake by interfering with GLUT4 mobilization; this mechanism may at least be partially responsible for the T2D onset in subjects chronically exposed to inorganic arsenic[271]. In a study[272] of 581 subjects, arsenic-linked hyperglycemia was related to insulin resistance, perhaps through arsenic-linked decrease of muscle mass, especially in females.

A study[231] exploring the associations of muscle arsenic concentrations with thyroid-related gene transcription in fish, testing the hepatic expression of genes including deiodinases D1 and D2, TTR, TRα and TRβ, found that arsenic levels were associated with TTR and TRβ, in the opposite direction of mercury effects. A study of 219 men found arsenic associated with a dose-dependent TSH increase and inversely associated with PRL[21]. Previous studies[21] reported arsenic inhibition of thyroid hormone synthesis and signaling enzymes. In a large Chinese cohort[273], prenatal arsenic exposure even at low level was inversely related to neonatal FT4 and positively related to neonatal TSH, indicating infant sensitivity to arsenic toxicity.

Reproduction

Arsenite is a metallo-estrogen; in a breast cancer cell line, it activated ER-α through an interaction with the hormone-binding domain

of the receptor and the action was blocked by an antiestrogen[274]. Most environmental exposures to metals do not occur in isolation, and the combined effects of metal co-exposures on HPG-axis are not well-known; a study[22] investigated in rats, after 15 days of drinking water with arsenic salt at 60 mg/L and manganese salt at 30 mg/L, the related co-exposure effects on reproductive hormones, sperm, and oxidative stress markers in brain, testes, and epididymis. The brain weight was unaffected, but fluid intake and testis' and epididymis' weights significantly decreased in all groups[22]. In comparison to the control group, a significant decrease in body weight gain was noted only in the co-exposed rats. The significant decreases of brain-, testes-, and epididymis-antioxidant status, and of FSH-, LH-, and testosterone-blood levels were similar after separate or combined exposure[22]. In the treated rats, compared to the untreated rats, a marked oxidative damage was noted joint to significant sperm quantity and quality decrease. Immediately after the exposure period, the changes persisted[22]. Thus, arsenic and manganese co-exposure suppresses the HPG-testicular axis and sperm function, likely *via* a mechanism of persistent oxidative stress and endocrine disruption[22].

In rats, sodium arsenite decreased LH and FSH levels, ovarian weight, and healthy follicle number; increased atresia[275,276]; decreased uterine size, uterine lumen invagination, epithelial-cells height, endometrial glands, and caused a thinner myometrium[275,276]. Also, sodium arsenite down-regulated RNA and protein expression of ER-α and vascular-endothelial-growth factor, an estrogen-responsive gene in the rat endometrium[276], and caused constant diestrous in rats[275,276]. In the anterior pituitary and uterus of ovariectomized rats, arsenic mildly reduced LH synthesis and release and augmented serum-PRL levels[277].

In women, arsenic was associated with decreased LH, decreased mature oocytes and oocyte yield following ovarian stimulation[60], and delayed menarche[278]. However, in a study[127] arsenic was not detected in any endometrial samples from women with or without infertility, and other studies[127,128] reported negative association of arsenic with fecundity and infertility.

Several scholars showed arsenic exposure and adverse pregnancy outcomes. In a study[279], arsenic in drinking water was associated with spontaneous abortions. However, another study[280] reported no association of arsenic urinary level with spontaneous abortion or stillbirth risk but detected increased infant mortality risk. Per other studies[281,282], maternal arsenic exposure early in pregnancy negatively influenced birth weight; maternal hair appeared to be a good measure of arsenic exposure, and maternal urinary arsenic metabolites concentrations were negatively associated with birth weight and gestational age. Another study[244] indicated for arsenic-exposed women a small risk for small-for-gestational-age infants. On the contrary, a study[283] in Inner Mongolia, China, reported that newborns born from areas with arsenic water exposure >100 μg/L were heavier than those born in areas with arsenic water exposure <20 μg/L. Different arsenic concentration and/or different metal co-exposure may provide distinct effects.

A study[284] of women of reproductive age compared pregnancy outcomes in women chronically exposed to arsenic in drinking water to those in unexposed women and found that 98% of the exposed women had been drinking water containing at least 0.10 mg/L arsenic and 43.8% had done so for 5-10 years, and rates of spontaneous abortion, stillbirth, and preterm birth were significantly higher in the exposed group.

However, a comprehensive review of studies[285] published between 1991-2012 did not find consistent evidence for positive associations between arsenic exposures and preterm birth.

Different studies' results may be due to different sample sizes and samples used to measure arsenic, as well as to genetic variations of populations. Also, different metal mixtures may trigger different effects and confound results.

Nickel and Its Effects

Industrialization is the major cause of nickel pollution. Forest fires, volcanic emission, and windblown dust are natural sources of nickel, while tobacco smoke, coal combustion, and waste incineration are artificial nickel emissions as well as dental and orthopedic implants, stainless-steel kitchen utensils and jewelry. Corrosion and leaching of pipes cause nickel to be in water[286]. Nickel was found at high doses in bottled drinking waters sold in Canada[287]. Nickel compounds are used also for batteries and in white gold, sterling, and German silver alloys.

Nickel is an essential element for vital functions, but increased exposure leads to toxic effects. Oral absorption of soluble nickel compounds is rapid but only 1-5% is absorbed; absorption and

clearance of insoluble nickel compounds from the lungs is slow, occurring over months; dermal absorption of nickel and nickel compounds from the skin is minimal; absorbed nickel is rapidly excreted from the urine, with a half-life of 20-60 hours. Oral exposure derives from water and food contaminated with nickel compounds[288]. EPA regulations state that the drinking water MCLs for nickel are 100 μg/L.

Nickel induces damage to chromatin[289], DNA, and infidelity of DNA replication, inhibits DNA repair by binding to DNA and nuclear proteins[290], can activate protooncogenes *via* impaired gene expression[13], and is thus carcinogenic. It causes the formation of free radicals in humans, leading to DNA modifications, lipid peroxidation, and impaired calcium and sulfhydryl homeostasis. The primary mechanism of nickel toxicity is glutathione depletion and binding to protein sulfhydryl groups[291]. Nickel may, at the molecular level, replace essential minerals in metal-dependent enzymes, leading to impaired protein function. Nickel crosses cell membranes *via* calcium channels and competes with calcium for specific receptors. Nickel cross-links amino acids to DNA, leads to ROS formation, and mimics hypoxia. These changes may activate signaling pathways and transcription factors and alter gene expression and cellular metabolism[23]. A study[292] reported that nickel is an enhancer of ultraviolet ray-induced skin cancers in mice.

Nickel is toxic to the blood, immune system, nervous system[26], kidneys[293], and reproductive organs[23].

Allergy Effects

Nickel causes skin allergies[294,295]; studies[51] of contact allergy to nickel described flare-up reactions after systemic provocation. In a study[296], allergic contact sensitization to nickel was associated with loss of function mutations in the filaggrin gene, whose protein is crucial in skin barrier function. Delayed sensitivity to nickel also appears due to the orthodontic use of nickel compounds in the oral cavity[297].

Pulmonary Effects

Nickel causes lung fibrosis[294], pneumoconiosis, bronchiolitis[298], and asthma[286]. Nickel sulfate administration to rats significantly increased in the lung lipid peroxides, decreased all antioxidant enzyme activities, and induced a loss of architectural organization, bronchioles inflammation, alveolar congestion and cell hyperplasia, and lumen congestion[299]. Exposure to mixed nickel salts is carcinogenic[300] and causes lung and nasal cancer[294,301]. A study[302] in Taiwanese lung cancer patients indicated that nickel levels in lung tumors were significantly higher than those in normal lung tissue of healthy controls.

Cardiovascular Effects

Nickel may cause kidney and cardiovascular system poisoning[294]. In rats exposed to nickel sulfate, beyond lung damage, urine volume was significantly decreased, and blood urea nitrogen increased in the highest dose group[55]. Also, rats exposed for 18 months to nickel developed myocardial fibrosis[48].

Rats and mice exposed to nickel inhalation had higher hemoglobin levels, increased red blood cell levels, and packed cell volume percentage due to augmented erythropoietin synthesis in response to tissue hypoxia induced by nickel[294].

Endocrine-Metabolic Effects

Nickel causes damage in the liver; nickel sulfate causes the loss of hepatic architecture, extensive vacuolization in hepatocytes, fatty changes, eccentric nuclei, and Kupffer cell hypertrophy. Nickel-treated rats had a significant increase of serum cholesterol, low-density lipoprotein cholesterol, and triglycerides, and a significant decrease of serum high-density lipoprotein cholesterol[46].

A study[303] reported that nickel at 0.1 mM added either at the onset of stimulation with angiotensin II or one hour later potentiated angiotensin-induced aldosterone production by adrenal glomerulosa cells. Further, nickel induced in a dose-dependent manner benign and malignant pheochromocytomas in male rats and combined cortical adenomas and carcinomas in female rats. The pheochromocytoma incidence was significantly increased in the 0.4 mg nickel/m^3 male rat group[304]. As systemic hypoxemia due to lung inflammation and neoplasms reduces gas exchange and stimulates adrenal catecholamine secretion, the chronic catecholamine hyperactivity may have led to hyperplasia and neoplasia of the adrenal medulla; hence, lung fibrosis, lung inflammation, and hypoxemia may also have induced pheochromocytoma in a second male rat model[305].

Human studies showed controversial results regarding nickel effects on PRL secretion: a study[306] reported PRL increase with air low-level nickel exposure and another study[307] found no

association of nickel exposure with PRL concentration in women with PCOS, probably due to different nickel exposure sources and concentrations. In humans, a cohort study observed FSH and LH elevation and normal testosterone levels in nickel-plating workers with sexual disturbances, indicating compensated primary hypogonadism[308]. In girls between 8-13 years old, HMs such as nickel, arsenic, cadmium, and aluminum could decrease estrogen levels and nickel could delay breast growth and sexual maturation[309]. Between 96 PCOS patients and 273 control subjects, there were no differences in lead, cadmium, and arsenic concentrations; however, serum nickel and copper levels were significantly higher and zinc levels significantly lower in PCOS patients, and thus nickel, copper, and zinc may play a role in the PCOS pathogenesis[310].

Reproduction

As a metallo-estrogen, nickel activated in a human breast cancer cell line, as potently as estrogen, ER-α, stimulated cell proliferation, and induced expression of the estrogen-regulated gene progesterone receptor. An antiestrogen can inhibit the nickel stimulus on the receptor[61].

Nickel impairs mammalian reproductive functions; the reproductive toxicology of nickel affects the HPG-axis[23]. In male rats, at the neuroendocrine level, nickel increased the concentrations of PRL[311].

In ovariectomized rats, pretreated with progesterone and estrogen, nickel compounded with LH-releasing hormone (LHRH) was more potent than LHRH alone in causing the FSH response[312]. In porcine pituitary cells, nickel compounded with gonadotropin-releasing hormone (GnRH) increased *via* the GnRH receptors the LH response more potently than GnRH alone and *via* a different intracellular mechanism[313]. In male mice, there was a dose-related depression in human chorionic gonadotropin-stimulated testosterone production of Leydig cells in culture following either *in vivo* or *in vitro* nickel treatment at a dose not inducing any toxicity, starting with nickel ≥125 mcM, with a noted time- and concentration-dependent effect[314].

Nickel increases both ovarian and testicular lipid peroxidation and induces histopathological changes in male and female reproductive organs[23]. In mice, nickel salts decreased weights of testes, epididymis, seminal vesicles, and prostate glands; reduced sperm motility and count; and caused sperm abnormalities[315]. In mice, nickel compounds increased antioxidant enzymes; caused dose-dependent lipid peroxidation in testis and epididymal sperm, dose-dependent increase of double-stranded DNA in testis and epididymal spermatozoa, and dose-dependent increase of percentage of abnormal sperm; and increased male-mediated dominant lethal-type mutations. The testicular toxicity is likely due to enhanced production of ROS, mediated *via* oxidative damage to macromolecules and DNA[316]. In a study[317], *in vitro* bovine spermatozoa exposed to nickel had significantly decreased motility after 120 and 240 minutes of culture, respectively, at nickel 1000 mcM and 500 mcM. Nickel at 125 mcM stimulated spermatozoa motility after 30 min, but later inhibited it. Significant alteration of spermatozoa membrane integrity was noted[317].

In a study[318] of female mice, nickel exposure caused a significantly lower implantation frequency and a smaller size of the litters. Nickel injection reduced body weights in fetuses. Nickel-treated mice had more frequent early and late resorptions, stillbirths, and abnormal fetuses[318].

Nickel crosses the human placenta, and its teratogenic and embryotoxic effects are mediated by lipid peroxidative damage to the placental membrane, which may cause impaired placental permeability, reduced placental viability, and embryotoxicity[319]. Nickel can insult the mammalian embryo directly and indirectly *via* maternal damage. Nickel may alter the maternal hormones and impair the development of the preimplantation embryo. Nickel can increase prenatal and neonatal mortality. It can produce different malformations in the surviving embryo; its teratogenicity appears delayed, probably due to retarded placental transfer[320]

Multiple Heavy Metals Interactions

Multiple Toxic Metals Effects

It is important to note that we do not yet know how the human body responds to multiple simultaneous toxins. Observations confirm that the body's defensive and elimination mechanisms may be sufficient to control most neurotoxins and toxins in general for the majority of the population, but synergistic factors between various trace metals have been reported[321].

Low-dose, long-term exposure to individual toxic metals is known to have deleterious effects. However, scarce information exists on how low-dose toxic-metal mixtures interact with toxic and

essential metals. Some synergistic effects for arsenic, lead, and cadmium have been reported[321]. A study[322] in mice reported the interactions between low-dose mixtures of lead, mercury, arsenic, and cadmium, and toxic and essential metals. Exposure to lead and cadmium increased brain lead by 479% in 30 days; lead plus mercury, arsenic and cadmium reduced liver mercury by 46.5% and increased kidney arsenic by 130% in 30 days; brain copper increased by 221% upon lead plus mercury, arsenic, and cadmium exposure; and liver calcium reduced by 36.1% upon lead and mercury exposure in 60 days[322]. Thus, the interactions within metal mixtures are largely synergistic. Also, low-dose metal exposures greatly influence levels of mercury in the brain and liver, and arsenic in the brain[322]. The influence exerted on essential metals was highest in the liver followed by kidney and brain[322]. Thus, low-dose metal mixtures exposure in tissues of mice affects toxic and essential metals homeostasis[322].

Lead, arsenic, and manganese are neurotoxic and often occur in mixtures for which we do not have markers to evaluate exposure and effects. Exposures to these metals may increase delta-ALA, which per se may potentiate neurotoxicity. A study[323] showed that the urinary delta-ALA levels (Delta-ALA-U) are a sensitive marker of neurotoxicity due to exposure to lead, arsenic, and manganese metal mixture. Co-treated rats showed a significant association of increased lead, arsenic, manganese, and delta-ALA levels in the brain and decreased motor activity. Delta-ALA-U concentrations were higher in the mixture treated group than the sum of the delta-ALA-U levels in each single treated group. Delta-ALA-U correlated with brain delta-ALA levels. Treatments with this metal mixture exacerbated behavioral dysfunction, increasing most prominently brain lead levels[323].

Metal-Metal Interactions (Figure 1)

Metals affect human health adversely through both direct action and mutual interactions. To characterize how different metals interact with each other in the human body, we conducted a pilot study (unpublished) of metal intoxication in an Italian cohort of healthy adult volunteers (N = 16). Pairwise correlation analysis of twenty urinary metals suggested that some metals were highly correlated with others. For example, aluminum displayed a tight negative correlation with mercury (-0.55, p = 0.027) but a remarkable positive correlation with nickel (0.79, p = 0.00026). Of all possible pairs, about 10% were statistically significantly correlated with each other. To better characterize how metals upon chelation affect each other, we constructed Bayesian networks for pre- and post-chelation (Figure 1). Bayesian networks are a commonly used approach and have been widely used to infer directed acyclic networks among interactive variables[324]. Following Musella's procedure, we

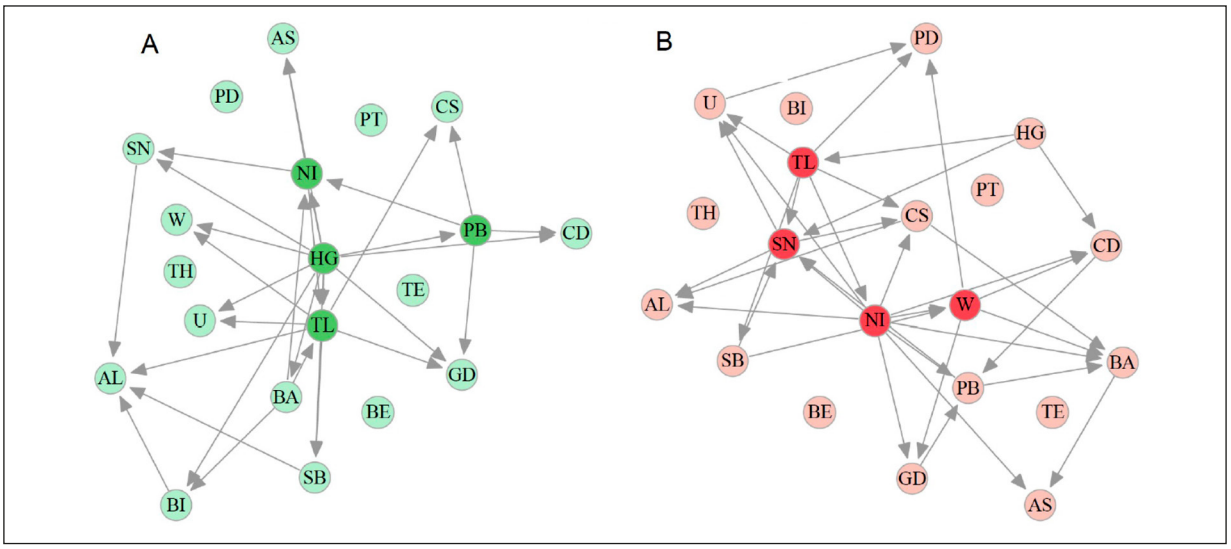

Figure 1. Bayesian network of metal-metal interaction pre-chelation (**A**) and post-chelation (**B**). Bolded symbols are hub metals that mediate the action of other metals. Arrows indicate the direction of influence. Aluminum (AL), antimony (SB), arsenic (AS), barium (BA), beryllium (BE), bismuth (BI), cadmium (CD), cesium (CS), gadolinium (GD), mercury (HG), nickel (NI), palladium (PD), platinum (PT), tellurium (TE), thallium (TL), thorium (TH), tin (SN), tungsten (W), uranium (U).

constructed the network of metal-metal interactions[324]. The network of metal-metal interactions differs structurally and organizationally between pre- and post-chelation. At pre-chelation, mercury, nickel, lead, and thallium served as hub metals that mediate the action of many other metals (Figure 1A). However, at post-chelation, thallium, tin, nickel, and tungsten became the hub metals that mediated the action of the metal-metal interaction network (Figure 1B). These data show how each HM may direct the clearance of, or interaction with, other HMs or be influenced by the presence of one or a few other HMs. This observation is relevant when studies are planned to investigate the role, accumulation, clearance, effects, and direction of action of HMs. The intricate interaction will be elucidated only by using innovative, sophisticated statistical tools, taking into account all HM variables.

Our Hypothesis (Figure 2) – Investigational Needs

It is highly probable that organisms may respond differently to toxins based on their genetic predisposition[208]. We know, for instance, that genetics, environment, and nutrition interact and lead to arsenic-related cardiovascular effects[257-259]. Although genetics, lifestyle, nutrition, and the microbiome may contribute to how humans respond to the toxic insults of HMs[325], we hypothesize that individuals become susceptible at a certain HM threshold which induces testable biological damage and development of disease states. However, beyond duration, the stage of development when exposure occurs will matter, especially for the brain. Prenatal, post-natal, childhood, adolescent, and adult exposure will each have different implications. The HM exposure threshold will be a function of the quantity of exposure to each metal, and it will also depend on the synergistic interaction among the various metals. Very limited data have correlated HM exposures to markers of biological and clinical aging in humans. We believe that studies are needed to test the single, additive, and synergistic dysfunctional effects of HMs and to identify on a continuum the threshold of toxicity of the combined metals as well as their ability to derange metabolic or biological markers and contribute to clinical, identifiable traits.

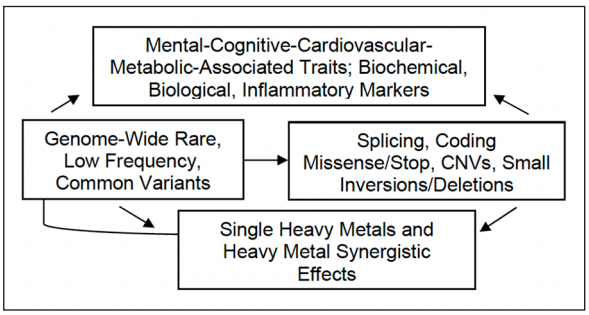

Figure 2. Hypothesized interaction between genetics, heavy metals, and pathology. Hypothesized causal heavy-metal toxicity interacting with genome wide-variants of different frequencies and nature and contributing to mental-cognitive-cardiovascular-metabolic-associated traits, and biochemical, biological, and inflammatory markers promoting aging.

We need a genetic, population-based, sample study testing: the impact of single, complex, and polygenic variants on the heavy-metal toxicity effects, and, the impact of haplotypes, diplotypes, and multilocus alleles, beyond genotypes and alleles, as predisposing risk factors for the HM toxicity burden and the mediated-biochemical and clinical effects. We also need to develop and apply innovative statistical models to test the genome-wide (GW) variant actions on HM accumulation and examine their role in the interaction between HM and biochemical clinical traits, as well as the GW-variants' possible mediation of the HM toxic effects. Importantly, we ought to test the additive versus synergistic function of HMs, report the toxic threshold, and estimate age- and sex-related genetic effects on biological and clinical traits.

We advocate for an interdisciplinary approach integrating GW-human genetics with the characterization of clinical biochemical and biological traits not commonly studied jointly within the novel toxicology setting of low-chronic HM exposure. This would lead to understanding and determining the role of HM toxicities in biological inflammation and aging and the HM contribution to biochemical and clinical traits, possibly with a new focus on mental-metabolic dysfunctions characterizing pre-disease states. By considering the HM-related possible pathogenesis of apparently different traits and biological parameters, the research of these traits and their related diseases would be dramatically advanced. Attention would shift towards: HMs acting in synergy as well as single metals as potential contributors to inflammatory processes, accelerated aging, and deranged psychological, cardiovascular, and metabolic traits, possibly with an increased toxic

load in subjects more genetically predisposed to HM toxicity. This could open a new horizon of diagnostic, clinical, and interventional approaches, including implementation of environmental safety tools as well as targeted detox therapies in individuals showing HM burden above a given safe threshold.

Conclusions

Living systems in the natural environment are simultaneously exposed to a variety of HMs with diverse physical and chemical properties. Many factors determine the way in which different metals influence the total toxicity, including metal concentration, mechanisms of metal action, and metal-organism interactions. In this review article, we presented a systematic survey of how different HMs impact human health. We performed a detailed analysis of biochemical, physiological, and pathological mechanisms underlying toxic effects of HMs on aging, chronic disorders, and fertility. We argue that a general model is needed to visualize, quantify, and coalesce metal-metal interactions, a pervasive but mostly neglected phenomenon, into informative and organized networks. These networks can interrogate how metal mixtures modulate toxic change across a range of environmental domains. Existing approaches aim to characterize the risks of HMs based on concentration addition models, failing to reveal the complex mechanisms of metal interactions. This network-based approach could provide a powerful means of standard regulatory assessment of the risk of environmental mixtures that previously was considered an insurmountable task.

In nature, complex interactions between metal toxicity and organisms occur; i.e., different metals are detrimental to an extent depending on the type of organisms. The model can be extended to incorporate information about metal-organism interactions. We are in the midst of an omics data revolution. By implementing toxicokinetic and toxicodynamic endophenotypes that link metal actions to end-point toxic phenotypes, the modified model could help to characterize a more comprehensive and mechanistic picture of metal toxicity useful for managing and maintaining long-term health within our environment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

C. Gragnoli conceived the study, reviewed the literature, drafted the manuscript, and performed the pilot study, M. Perrelli revised the literature, drafted the manuscript, and performed the pilot study. Rongling Wu analyzed the data and participated in the writing. Laura del Bosque-Plata, Dajiang Jeff Liu, Jurg Ott, Roberto Giuseppe Lucchini, Michael John Vergare, and Mohammed Pervez Akhter. searched the literature and critically revised the manuscript.

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