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Toxic Effects of Environmental Heavy Metals on Cardiovascular Pathophysiology and Heart Health Function: Chelation Therapeutics

Loutfy H. Madkour

Department of Chemistry, Faculty of Science and Arts, Baljarashi, Al Baha University, Baljarashi 65635, Saudi Arabia.

Abstract

The mobilization of heavy metals by man through extraction from ores and processing for different applications has led to the release of these elements into the environment. Since heavy metals are non-biodegradable, they accumulate in the environment and subsequently contaminate the food chain. This contamination poses a risk to environmental and human health. Heavy metals are strongly implicated in atherosclerotic heart disease. There is many evidence supporting toxic xenobiotic heavy metals as an emerging cardiovascular risk factor. In this review, we will summarize the evidence for the four toxic xenobiotic heavy metals such as lead, cadmium, mercury and arsenic that are chelated most effectively by edentate (EDTA) disodium and that have convincing published reports documenting their cardiovascular toxicity ranked priority, as environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry. The metabolic effects of heavy metals and hypothetical mechanisms of metal toxicity are discussed. Standard therapies involving treatment with EDTA and curcumin as chelating agent for heavy metals are given. EDTA normalizes the distribution of most metallic elements in the body. There is a relationship between heavy metals to the blood pressure and cholesterol level as a risk factor of myocardial infraction, coronary or cardiovascular disease. Xenobiotic heavy metals (Pb, As, Hg and Cd deplete glutathione and protein-bound sulfhydryl groups, resulting in the production of reactive oxygen species as superoxide ion, hydrogen peroxide and hydroxyl radical ($O_2^{\cdot-}$, H_2O_2, $^{\cdot}OH$, OH^-), consequence, enhanced lipid peroxidation and DNA damage. Curcumin reduces the toxicity induced by xenobiotic heavy metals due to its scavenging and

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Correspondence to: Madkour LH, Department of Chemistry, Faculty of Science and Arts, Al Baha University, Baljarashi 65635, Saudi Arabia.
Email: loutfy_madkour@yahoo.com, Lmadkour@bu.edu.sa lha.madkour@gmail.com; Phone: +966533899075

chelating properties. The genetic mechanisms through which heavy metals act to increase cardiovascular disease CVD may act still remains unknown. However, additional research is needed in order to propose the exact mechanism of CVD induced by heavy metals.

Key words: Heavy metals, Cardiovascular disease, Oxidative stress, EDTA, Curcumin chelation.

1. Introduction

The mobilization of heavy metals such as Pb, Zn, Cu, Fe, Mn [1-7]; Sb [8, 9]; Sn [10,11]; Ti [12]; In [13]; U [14] and many others by man through extraction from its natural ores and processing for different applications has led to the release of the elements into the environment. Since heavy metals are no biodegradable, they accumulate in the environment and subsequently contaminate the food chain. This contamination poses a risk to environmental and human health. Metals are notable for their wide environmental dispersion from such activity; their tendency to accumulate in selective tissues of the human body; and their overall potential to be toxic even at relatively minor levels of exposure. Some metals, such as copper and iron, are essential to life and play irreplaceable roles in, for example, the functioning of critical enzyme systems. Heavy metals, and repairable particulate matter (PM2.5 and PM10), differ in their chemical composition, reaction properties, emission, time of disintegration and ability to diffuse in long or short distances. It ranges from minor upper respiratory irritation to chronic respiratory and heart diseases. Thus remediation of heavy metal pollution deserves due attention. Detrimental effects of heavy metals on the cardiovascular system have been less well defined.

1.1. *Metal pollutants and cardiovascular disease (CVD)*

Metals, a major category of globally-distributed pollutants, are natural elements that have been extracted from the earth and harnessed for human industry and products for millenia (An exception to metals being "natural" is plutonium, the material at the heart of nuclear weapons, created by man through the processing of uranium). There is epidemiological evidence that metal contaminants may play a role in the development of atherosclerosis and its complications. The association of environmental pollutants, including metals, with cardiovascular disease has been reviewed elsewhere [15-17]. There is strong evidence that xenobiotic metal contamination is linked to atherosclerotic disease [18-19] and is a modifiable risk factor. This is, therefore, an opportune moment to review the causal link between metal pollutants and cardiovascular disease (CVD). Cardiovascular disease (CVD) is the leading cause of mortality in the industrialized world. In the United States alone, it kills 1 million people per year; accounting for over 40% of alldeaths [20, 21]. More alarmingly, CVD is rapidly becoming a major cause of death worldwide, and current projections indicate that between 1990 and 2020, the proportion of worldwide deaths from CVD will increase from 28.9% to 36.3% [22]. With the ominous increase in the incidence of diabetes and obesity, both of which profoundly affect cardiovascular health [23], the total burden of CVD in the future may be even greater. Although intensively studied, the reasons underlying the high incidence of CVD remain unclear. Several "risk factors" have been associated with the development of CVD, but it is sobering to consider that many patients suffering from heart disease have no established risk [24], suggesting that quantitatively important determinants of CVD are currently unknown [25]. The development of CVD is a result of a chronic and complex interplay

between genetic and environmental factors. Whereas genetic makeup is a critical determinant (related to a set of non-modifiable risk factors such as age, sex, family history, height, and postmenopausal status in women), large changes in the incidence of CVD over the last century indicate that environmental influences are also as important. Multiple studies show that non-genetic factors such as diet, smoking, physical activity, and alcohol intake significantly modify CVD risk [21]. In addition, it has been reported that migration of genetically similar populations to new environments alters CVD risk [25], indicating that heart disease is not an inevitable fate of an aging population, but that its development is profoundly modified by the environment. Other contributors of risk, e.g., elevated low-density lipoprotein (LDL) cholesterol, hypertension, diabetes, obesity, reduced high-density lipoprotein (HDL), lipoprotein a, fibrinogen, homocysteine, plasminogen activator inhibitor, and left ventricular hypertrophy are a combination of environmental and genetic factors. Indeed, the term "risk factor" was coined by the Framingham group investigating the epidemiology of CVD [21]. Since then there have been extensive and ongoing efforts to establish that environmental factors contribute to the induction, progression, and severity of CVD; although a clear role of environmental pollutants in affecting heart disease is only now beginning to emerge. There are multiple reasons for the delayed appreciation of cardiovascular toxicity as a significant outcome of pollutant exposure. Whereas some of these reasons relate to historical chance or bias, others may be related to the difficulty in demonstrating small changes in CVD risk over the high background levels of the disease. Added to this is the experimental difficulty in demonstrating the effects of pollutants on CVD because only the severity and progression, rather than induction, of the disease are likely to be affected. Such demonstrations require well-established animal models of ongoing CVD, some of which have become available only in the last few years. Blood is fed to the heart muscle by the coronary arteries as shown in Figure1. Finally, because the heart and blood vessels are neither the site of primary exposure (as lung, gut, or skin) nor of metabolism and detoxification (e.g., kidney or liver), it has been tacitly assumed that cardiovascular tissues suffer less from exposure to environmental toxins. This assumption is, however, not supported by extensive data demonstrating robust cardiovascular effects of environmental pollutants [20].

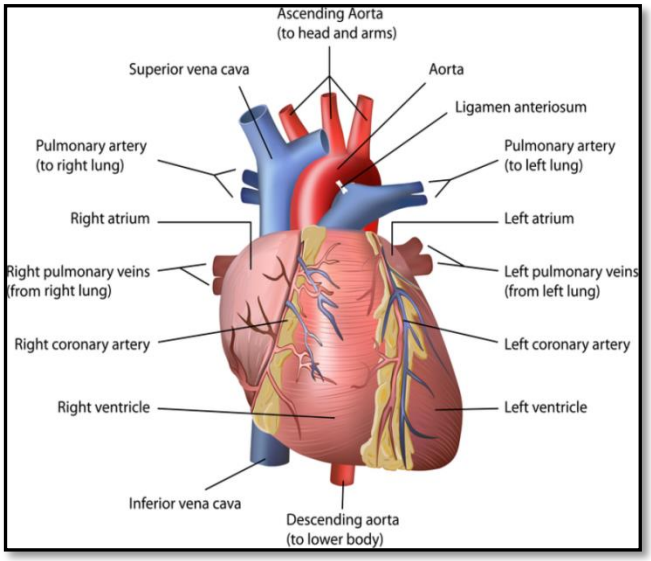

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Figure 1. Blood is fed to the heart muscle by the coronary arteries. Veins return blood to the heart from the extremities. Blood is then pumped to the lungs to become oxygenated, and then back to the heart to be pumped out again– multiple thousands of times a day.

1.2. *Link between air pollution and heart disease*

Heart failure deaths, which make up 10% of all cardiovascular deaths, accounted for 30% of cardiovascular deaths related to PM toxicity [26].

1.3. *Particulate matter (PM) composition and metal toxicity*

Several reports suggest that much of PM toxicity is related to the transition metal content of the particles. For instance, in rats subjected to intratracheal PM instillation, the lung dose of bioavailable transition metals, but not instilled PM mass, was the primary determinant of the acute inflammatory response [27]. In agreement, some investigators studying the direct effects of PM on cells in culture have reported that PM generated oxidants and toxicity are prevented by removing metals or by metal-chelating agents [28-31]. Collectively, these studies are consistent with the view that PM exposures result in the delivery of metals to multiple extra- pulmonary sites where they form reactive centers that continually catalyze the generation of reactive oxygen species and induce oxidative stress. Whereas PM-associated metals in general may be toxic, the role of specific metals is less well understood. Several PM associated metals have been tested for their contribution to toxicity. Universally high toxicity has been attributed to vanadium, although the Ni, Cu, Fe, and Zn content of PM has also been linked to selective measures of toxicity in a tissue-specific manner [32-34]. For cardiovascular exposures in particular, Ni has been linked to the cardio depressant effects of ROFA exposure [35, 36] and changes in HRV have been correlated with V and Pb content in broiler workers [37]. Clearly, further work is warranted, not only to elucidate the role of metals in PM toxicity, but also to study the effects of environmental transition metals on CVD in general. To date little is known in regard to mechanisms by which non-particulate exposure to environmental metals affects cardiovascular health. Basics of metal delivery and deposition in cardiovascular tissues remain largely unknown, although studies with Ni [38], Cr [39], Hg [40], and Cd [41] show that environmental exposure to these metals results in their deposition in the heart and blood vessels, and that the cardiovascular tissues are significant targets of metal toxicity. Moreover, the cardio toxicity of transition metals, heavy metals, and metalloids is well known. Long-term arsenic exposure is associated with peripheral vascular disease and with an increase in the incidence of ischemic heart disease [42]. Exposures to cadmium are associated with arterial hypertension in men [43] and young monkeys [44] and increases aortic resistance in rabbits [45]. Interestingly, large increases in myocardial trace element concentration have been observed in cases of idiopathic dilated cardiomyopathy [39]. Furthermore, an increase in the incidence of heart failure in Japanese inhabitants of an area polluted by cadmium has been reported [46]. These observations underscore the relevance of metal pollutants (in air particulates or drinking water) to CVD risk while at the same time point toward a greater need for understanding the metabolism of exogenous as well as endogenous trace metals (particularly Fe and Cu) and how they affect CVD. Because excess mortality associated with PM is largely related to cardiopulmonary deaths, the contribution of CVD to the overall health burden of pollution is likely to be numerically significant.

2. Definitions

2.1. *Heavy metals*

Heavy metals are naturally occurring elements that have a high atomic weight and a density at least 5 times greater than that of water. Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment, raising concerns over their potential effects on human health and the environment. The most commonly used terms for metal pollutants, heavy metals or toxic heavy metals, refer to specific density, atomic weight, atomic number, or other chemical properties. We have chosen to use the term xenobiotic, to denote a foreign chemical substance found within an organism, thus, xenobiotic metal. Heavy metals [47] are commonly defined as those metallic elements with high atomic weight such as arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb) and mercury (Hg) that may damage living organisms at low concentrations and that tend to accumulate in the food chain [48,49]. They enter to the human body by ingestion, inhalation or through the skin and their presence may cause serious toxicity [50, 51]. Sources of exposure to these metals include occupational exposure and environmental contamination from industrial production with poor emission and disposal practices [52-55]. The principal metal emission sources come from the following industries: petrochemical, extractive, and metallurgic (foundry and metallurgy), mechanic (galvanic processes, painting), chemical (paints, plastic materials) and ceramic [56]. Exposure to compounds containing heavy metals is known to be toxic, mutagenic, teratogenic and carcinogenic to human beings and diverse animals (Figure 2) [57-59].

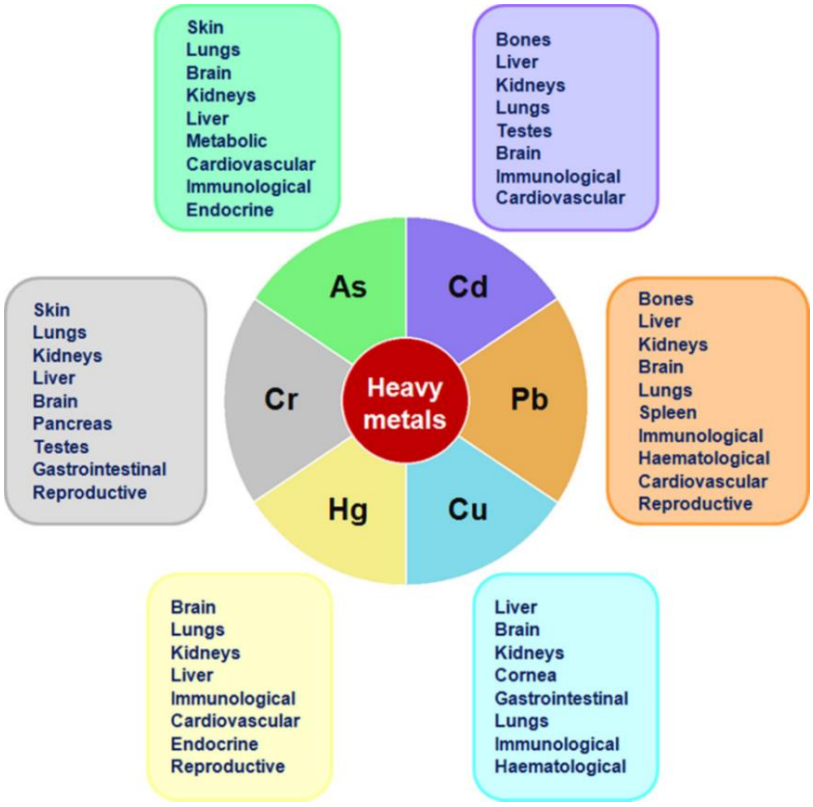

Figure 2. Main organs and systems affected by environmental or occupational exposure to heavy metals.

2.2. *Xenobiotic metals*

Xenobiotic metals have no biological role at any dose. These include lead, arsenic, mercury, cadmium, and many others. We will focus on these 4 toxic, xenobiotic metals that are ranked among the top 10 on the current Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances [59]. Arsenic, lead, and mercury are ranked as the top 3 hazardous substances.

Heavy metals are xenobiotic, that is, they can be found in the body but have no known biological function [60]. These include lead, arsenic, mercury, cadmium, and many others [18, 47-49, 51, 58, 61]. Xenobiotic have no useful role in human physiology (and most other living organisms) and, even worse, as in the case of lead and mercury, may be toxic even at trace levels of exposure. Even those metals that are essential, however, have the potential to turn harmful at very high levels of exposure, a reflection of a very basic tenet of toxicology-"the dose makes the poison." One reflection of the importance of metals relative to other potential hazards is their ranking by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), which lists all hazards present in toxic waste sites according to their prevalence and the severity of their toxicity. The first, second, third, and sixth hazards on the list are heavy metals: lead, mercury, arsenic, and cadmium, respectively [15, 18, 49, 51, 58-61]. Exposure to metals can occur through a variety of routes. Metals may be inhaled as dust or fume (tiny particulate matter, such as the lead oxide particles produced by the combustion of leaded gasoline). Some metals can be vaporized (e.g., mercury vapor in the manufacture of fluorescent lamps) and inhaled. Metals may also be ingested involuntarily through food and drink. The amount that is actually absorbed from the digestive tract can vary widely, depending on the chemical form of the metal and the age and nutritional status of the individual. Once a metal is absorbed, it distributes in tissues and organs. Excretion typically occurs primarily through the kidneys and digestive tract, but metals tend to persist in some storage sites, like the liver, bones, and kidneys, for years or decades. Additional, less readily quantifiable, cardiovascular [20] burden of pollution may be related to pervasive changes such as hypertension or dyslipidemia that have been shown to be caused by exposure to xenobiotic metals. Collectively, these data raise the possibility of an etiologic relationship between chronic pollutant exposure and hypertension or hypercholesterolemia and could partially account for the endemism of CVD in the industrialized world. Not only could pollutants exacerbate and accelerate CVD, risk factors associated with CVD could predispose and sensitize for pollutant toxicity. Thus preexisting CVD in itself could be a risk factor of environmental toxicity. Chronic hypercholesterolemia, for instance, could significantly affect xenobiotic metabolism and disposition by either altering the expression of detoxification enzymes in liver and peripheral tissues or by providing additional circulating nucleophilic binding sites (e.g., lysine residues of apolipoprotein and ethanolamine phospholipids). Moreover, interaction with lipoprotein nucleophiles could decrease xenobiotic clearance and deliver xenobiotic to otherwise inaccessible vascular sites, prevent receptor-mediated lipoprotein clearance, and dysregulation lipoprotein metabolism [20]. We will focus on the four toxic, xenobiotic metals: lead, cadmium, mercury and arsenic that are ranked among the top 10 on the current Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances [59]. Arsenic, lead, and mercury are ranked as the top 3 hazardous substances. These

metals are extremely toxic, although very low concentrations of them may be hermetic [15, 18, 49, 51, 60-61].

3. Heavy metals and oxidative stress

Oxidative stress [62] is a highly seasonal phenomenon in bivalve mollusks. The modulation of oxidative stress by environmental pollutants is a factor which could seriously complicate interpretation of biomonitoring data. Laboratory and field studies [62] have suggested that measurements of the levels of the proteins may be indicative of exposure to chemical pollution. Another important set of investigations have focused on bio-indicators of oxidative stress within the organisms. Such studies suggest that oxidative stress may render mussels more sensitive to toxicity from xenobiotics. Because of the ability of heavy metals to exist in a variety of oxidation states, metals are capable of becoming involved in processes leading to oxidative stress in mollusks. The two most commonly studied heavy metals are the cations iron and copper [63]. A variety of studies have demonstrated the ability of iron chelates or complexes to catalyze the formation of reactive oxygen species and stimulate lipid peroxidation. Aust [64] has reviewed the relationship between metal ions, oxygen radicals, and tissue damage. The role of iron in the initiation of lipid peroxidation has also been reviewed by Minotti and Aust [65] and Alleman *et al* [66]. These investigators have presented evidence that lipid peroxidation requires both Fe(III) and Fe(II), probably as a dioxygen-iron complex. Iron is capable of catalyzing redox reactions between oxygen and biological macromolecules that would not occur if catalytically active iron were not present. Iron complexed with adenosine 5'-diphosphate (ADP), histidine, ethylenediaminetetraacetic acid (EDTA), citrate, and other chelators has been shown to facilitate the formation of reactive oxygen species and enhance production of lipid peroxidation [64, 67]. Evidence indicates that chelated iron acts as a catalyst for the Fenton reaction, facilitating the conversion of superoxide anion and hydrogen peroxide to hydroxyl radical, a species frequently proposed to initiate lipid peroxidation [62, 68-69].

4. Fenton Reaction

$$Fe\ (III) + O_2^{\bullet -} \rightarrow Fe\ (II) + O_2 \quad (1)$$

$$Fe\ (II) + H_2O_2 \rightarrow Fe\ (III) + HO^- + {}^{\bullet}OH \quad (2)$$

However, criticisms have been levied against the involvement of Fenton reactions in vivo, and these have been reviewed in depth by Halliwell and Gutteridge [70]. The major criticisms are that the rate constant for the Fenton reaction is too low, the reactive oxygen species produced is not the hydroxyl radical, and there are no metal catalysts available in vivo. In response to these criticisms, calculations based on rate constants suggest that hydroxyl radicals may be generated at the rate of approximately 50 per cell per second, which could have enormous biological consequences. Several studies have suggested that ferryl, an iron-oxygen complex, is the reactive species formed, although the vast majority of evidence supports hydroxyl ion as the reactive oxygen species produced by the Fenton reaction [71]. In complex biological systems it is difficult to discriminate between hydroxyl radicals and ferryl species as the initiators of peroxidative reactions. Ample evidence exists that metal ions are required for hydroxyl radical formation, and these ions may be bound at specific sites that are not readily accessible to some scavengers and chelators [70]. Upon ingestion of iron, iron is both oxidized and stored in the iron storage protein ferritin or associates with the iron transport

protein transferrin in the blood stream. For iron to facilitate the formation of reactive oxygen species via the Fenton reaction, the iron must be in a free or catalytically active form. Most iron is complexed, and little free iron actually exists in nature. A variety of xenobiotics has been shown to facilitate the release of iron from ferritin, including paraquat, diquat, nitrofurantoin, adriamycin, daunomycin, and diaziquone [67]. Thus, a variety of xenobiotics may enhance the formation of reactive oxygen species not only by undergoing redox cycling, but may also facilitate the release of iron, which catalyzes the formation of reactive oxygen species. The preceding studies provide insight into the roleof reactive oxygen species in the toxicity of transition metals [63]. Similar mechanisms involving the Fenton-like production of superoxide anion and hydroxyl radical appear to be involved for iron, copper, chromium, and vanadium. However, with some metal ions, such as mercury, nickel, lead, and cadmium, depletion of glutathione and protein-bound sulfhydryls may play a primary role in the overall toxic manifestations.

$$M(X) + O_2^{\bullet -} \rightarrow M(X - 1) + O_2 \quad (3)$$

$$2\ O_2^{\bullet -} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (4)$$

$$M(X - 1) + H_2O_2 \rightarrow M(X) + {}^{\bullet}OH + OH^- \quad (5)$$

Increasing evidence indicates that multiple mechanisms may be involved in the production of reactive oxygen species. Fenton-like reactions may be commonly associated with most membranous fractions as mitochondria, microsomes, and peroxisomes. Phagocytic cells may be another important source of reactive oxygen species. Thus, a single transition metal may initiate formation of reactive oxygen species by more than a single mechanism, involving more than one organelle or cell type. The ability of zinc to reduce oxidative stress may be due to its ability to displace redox active metal ions from site-specific loci. Based on the evidence that has accumulated to date, the involvement of reactive oxygen species and/or free radicals may be common to the toxic mechanisms of most xenobiotic, although differences will exist in whether the formation of reactive oxygen species is an early, intermediate, or late event in the sequence of events leading to irreversible cell damage and death. It is becoming increasingly clear that reactive oxygen species are formed and play a role in the toxic manifestations of most xenobiotics. The damage to lipids, proteins and DNA, the role of thiols and antioxidants including vitamins A, E, and C, as well as the altered calcium homeostasis that occurs because of membrane damage, leading to activation of various calcium-dependent systems including endonucleases is explained. Furthermore, the amplification loop associated with tumor necrosis factor (TNF-α) and the roles of protein kinase C and stress proteins are depicted. Future studies will provide greater clarification of the complex interrelationships that are involved. Many of the inconsistencies and contradictions that appear to exist with respect to the role of reactive oxygen species in the toxicities of many xenobiotic, including transition metals, may be explained based on the toxic kinetic properties of each of the xenobiotic in question. The absorption of various xenobiotic, their distribution, compartmentation within cells, site-specific loci, microenvironments, localization of enzyme systems, and the cellular distribution of antioxidant defense mechanisms all contribute to differences that are observed with respect to the production and tissue-damaging effects of reactive oxygen species. With the advent of new technologies, numerous questions

regarding reactive oxygen species, their transport, tissue-damaging effects, and relative roles in the mechanistic sequences associated with toxicity and carcinogenicity will be answered. Many of the toxic effects [62] observed in marine animals exposed to high levels of heavy metals involve membrane- related processes. A possible mechanism for such toxicity is by metal-mediated peroxidation of lipid components of membranes because of oxyradicals. It has been demonstrated that Copper may cause a significant increase in malondialdehyde (an indicator of the peroxidative process) and a decrease in GSH while Cd and Zn do not [71]. This increase is associated with an elevation of the levels of lysosomal lipofuscin granules. It is clear from this that a complex relationship may exist between metals, their homeostasis [72], oxidative stress and seasonality. Varying levels of metals could be expected to lead to an altered oxyradical threat to cells. Possible effects of this on bio-indicator molecules would obviously need to be taken into account in biomonitoring studies. Toxic manifestations of these metals [47] are attributed primarily to oxidative stress [73]. Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, so-called oxidants, and their elimination by antioxidant systems. This imbalance leads to damage of important biomolecules and organs with potential impact on the whole organism [74]. The associated DNA, protein, and lipid damage may underlie liver diseases as a key pathophysiological force. The above may also be related to chronic liver injury, hepatic inflammation, and fibrosis and to hepatocellular carcinoma [75-76]. The liver is an important organ to be considered when the effects of pollutants are investigated, since this organ plays a central role in the metabolism and detoxification of biological substances. Also, most of the substances absorbed by the intestine pass first through the liver where toxins and heavy metals may accumulate [77]. Chromium and copper undergo redox-cycling reactions, while the primary route for the toxicity of arsenic, cadmium, lead and mercury is the depletion of glutathione (GSH) and bonding to sulfhydryl groups of proteins. But the unifying factor in determining toxicity and carcinogenicity for all these metals is the generation of reactive oxygen species (ROS) such as the hydroxyl radical ($HO^{\cdot}$), superoxide radical ($O_{2}^{\cdot -}$) or hydrogen peroxide (H_2O_2). The excessive ROS generation overwhelms the cell's capacity to maintain a reduced state [78-80]. Oxidative stress induced by metal exposure leads to the activation of the nuclear factor (erythroid-derived 2)-like 2/Kelch-like ECH associated protein 1/antioxidant response elements (Nrf2/Keap1/ARE) pathway [81], through the activation of numerous transducers such as mitogen-activated protein kinases (MAPK, ERK, p38), protein kinase C (PKC), and phosphatidylinositol3 kinase (PI3K) which phosphorylate both Nrf2 and Keap1 [82-85]. In addition, reactive electrophiles directly attack the sulfhydrylrichKeap1 protein, leading to conformational changes in their structure [86]. The cumulative impact of these events is the stabilization and activation of Nrf2 and transcriptional up-regulation of antioxidant genes protecting cells from heavy metal toxicity; and carcinogenesis from ROS and electrophiles [87-89]. Heavy metals generate many of their adverse health effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, and depletion of protein sulfhydryl's (e.g., glutathione) [79].

5. Cardiovascular system

Recent studies have shown that metals, including iron, copper, chromium, and vanadium undergo redox

cycling, while cadmium, mercury [19, 63] and nickel, as well as lead, deplete glutathione and protein-bound sulfhydryl groups, resulting in the production of reactive oxygen species as superoxide ion, hydrogen peroxide and hydroxyl radical. Consequently, enhanced lipid peroxidation, DNA damage, and altered calcium and sulfhydryl homeostasis occur. Fenton-like reactions may be commonly associated with most membranous fractions including mitochondria, microsomes, and peroxisomes. Carbon monoxide binds to haemoglobin modifying its conformation and reduces its capacity to transfer oxygen [90]. This reduced oxygen availability can affect the function of different organs (and especially high oxygen consuming organs such as the brain and the heart), resulting in impaired concentration, slow reflexes, and confusion. Apart from lung inflammation, systemic inflammatory changes are induced by particulate matter, affecting equally blood coagulation [91]. Air pollution that induces lung irritation and changes in blood clotting can obstruct (cardiac) blood vessels, leading to angina or even to myocardial infraction [92]. Symptoms such as tachycardia, increased blood pressure and anaemia due to an inhibitory effect on haematopoiesis have been observed as a consequence of heavy metal pollution (specifically mercury, nickel and arsenic) [93]. Finally, epidemiologic studies have linked dioxin exposure to increased mortality caused by ischemic heart disease, while in mice, it was shown that heavy metals can also increase triglyceride levels [94].

5.1. *Cardiovascular effects of lead*

Lead is stored in the bone but may affect any organ system. Increased death from CVD is strongly associated with bone lead levels. People with the highest bone lead levels [18, 95] are nearly 10 times more likely to die of ischemic heart disease than those with the lowest. Lead levels are directly associated with higher blood pressure, cholesterol abnormalities, and atherosclerosis (plaques clogging the arteries of the heart). Increased cardiovascular mortality has been attributed to both elevated blood and bone lead levels with stronger association for bone levels [96, 97]. Weisskopf *et al* [98] analyzed the association between tertiles of patella and tibia lead and mortality in 868 male participants of the Veterans Affairs Normative Aging Study. Lustberg and Silbergeld [99] reported that subjects with blood lead levels of 20 to 29 µg/dL had increased all-cause mortality compared with those having blood lead levels <10 µg/dL. Menke *et al* [99] found that the risk of cardiovascular events was significantly greater in participants with the highest tertile of lead exposure (≥0.17 µmol/L or 3.62 µg/dL), compared with those in the lowest tertile (< 0.09 µmol/L or 1.94 µg/dL). The NHANES survey (1999-2000) showed that blood lead was associated with an increased prevalence of peripheral arterial disease (PAD), even at levels below current safety standards [96]. The association of lead exposure with hypertension is one of the best established cardiovascular effects of this metal [101,102]. Lead exposure has also been linked to dyslipidemia and atherosclerosis [99, 103-104]. Experimental and human autopsy studies showed an association between lead exposures and aortic atherosclerotic plaque burden [99, 104-106]. There are some interesting findings that support the association of lead with atherosclerosis. For example, the cardio protective antioxidant activity of high-density lipoprotein is partially mediated by paraoxonase activity, an enzyme that is closely bound to the high-density lipoprotein particle and involved in inhibition of low-density lipoprotein (LDL) oxidation. Lead as well as other metals can inactivate paraoxonase and,

therefore, promote LDL oxidation and atherosclerosis development [107-109]. Lead and cadmium, are ranked second and seventh, respectively, as environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry [110]. The possible association between lead and cardiovascular disease has been recognized for many years [111-113]. The most robust studies evaluating the association of blood lead with cardiovascular outcomes have been conducted using data from the National Health and Nutrition Examination Surveys (NHANES). NHANES studies reported that despite the remarkable drop in blood lead following the elimination of leaded gasoline, blood lead levels remain associated with cardiovascular outcomes of atherosclerotic origin, including coronary heart disease, hypertension, stroke, and peripheral arterial disease [96, 114]. Cumulative lead exposure, as reflected by bone lead, and cardiovascular events have been studied in the Veterans' Normative Aging Study, a longitudinal study among community-based male veterans in the greater Boston area enrolled in 1963. Patients had a single measurement of tibial and patellar bone lead between 1991 and 1999 [115]. The HR for ischemic heart disease mortality comparing patellar lead >35 to <22 μg/g was 8.37 (95% CI: 1.29 to 54.4). Lead is an established risk factor for hypertension on the basis of consistent epidemiological evidence in populations around the world, as well as experimental evidence showing increases in blood pressure levels in animal models [113, 116]. Substantial in vivo and in vitro evidence supports that lead reduces nitric oxide bioavailability [117], as well as promotes oxidative stress and inflammation. These mechanisms are believed to play a major role in lead-related vascular disease (Central Illustration). In experimental models, lead-induced hypertension was reversible, either with a chelating agent or with antioxidant treatment [117]. Recent studies suggest that there may be epigenetic modifications due to lead exposure, for instance, with hypomethylation in a promoter of the *COLIA2* gene [118].

5.2. *Cadmium and cardiovascular disease*

Several studies have evaluated the association between cadmium and cardiovascular disease in the general U.S. population using NHANES data [119-121]. In NHANES 1988 to 1994, for every doubling of urine cadmium, there was a 36% increase in coronary heart disease mortality in men, but no increase was observed in women. In NHANES 1999 to 2004, however, blood and urine cadmium were associated with increased cardiovascular disease mortality, including coronary heart disease, in both men and women. In the Strong Heart Study, participants with diabetes showed stronger associations between cadmium and CVD outcomes than did those without diabetes, and the difference was statistically significant [122]. Cadmium exposure has also been related to peripheral arterial disease. In NHANES analyses, it was proposed that cadmium could potentially mediate at least part of the effect of smoking on peripheral arterial disease [121]. A recent systematic review concluded that the evidence supports the role of cadmium as a cardiovascular disease risk factor, especially for coronary heart disease [123]. Cadmium is thought to promote atherosclerosis through oxidative mechanisms [124]. Cadmium can indirectly deplete antioxidants, such as glutathione, increasing reactive oxygen species (Central Illustration) [125]. Subclinically, cadmium has been related to early atherosclerosis, including higher carotid intima-media thickness and carotid plaque in

women from Europe [124]. In experimental studies, low-level cadmium exposure can increase endothelial permeability, inhibit proliferation of endothelial cells, and induce cell death. Cadmium has also been related to gene expression and differential methylation in genes encoding proteins involved in longevity, cardiovascular disease severity, and vascular calcification (RASAL1 and Klotho) [126-127]. Cadmium is associated with cardiovascular and all-cause mortality. Menke *et al.* [128] reported that every 2-fold increase in creatinine adjusted urinary cadmium levels in men is associated with an increase in risk of all-cause and cardiovascular mortality. The risk of coronary artery disease (CAD)–associated mortality was also increased. Studies showed cardiovascular mortality to be associated with urinary cadmium levels in both genders [116-117]. In a review published recently by Tellez- Plaza *et al* [118] based on 12 studies the pooled relative risk (RRs) for CVD, CAD, stroke, and PAD for men and women were modest in magnitude but quite consistent. Cadmium has also been associated with PAD in both men and women [118, 129-131].

5.3. *Mercury and cardiovascular disease*

When evaluating the association of mercury levels and CVD, it is important to note that this relationship may be confounded by fish consumption, which raises mercury levels but lowers cardiovascular risk. In 1995, Salonen *et al* [132] reported an association between high levels of mercury exposure via freshwater fish consumption and risk of acute myocardial infarction (AMI), all-cause, and cardiovascular mortality. Men in interquartile range between 5.8 and 15.7 μg/g creatinine. The hazard ratios for CVD mortality, CAD mortality, and stroke mortality per interquartile range were 1.65 (95% CI 1.20-2.27; P < .001 for trend), the highest tertile of hair mercury content when compared to the lowest tertile had RR of fatal or nonfatal AMI of 1.69 (95% CI 1.03-2.76, P = .038), RR of CVD of 2.9 (95% CI 1.2- 6.6, P = .014), and RR of death from any cause of 2.3 (95%
CI 1.4-3.6, Pb .001). The RR of coronary death in this study was not associated with hair mercury content. In a case control study, Guallar *et al.* [133] showed an association between higher levels of toenail mercury and risk of nonfatal AMI. More recently, Mozaffarian *et al* [134] found no association between toenail mercury and CAD, stroke, or total CVD in participants with either normal or low levels of selenium, which may protect against mercury toxicity. Data regarding a relationship between mercury exposure and blood pressure changes are inconsistent [135-138]. Studies of chronic occupational mercury exposure in miners revealed a 46% increase in incidence of hypertension when compared to age-matched controls [139]. Correlations have been reported between hair or blood mercury and elevated blood pressure [135-136].

5.4. *Cardiovascular effects of arsenic*

There is only limited evidence on the relationship between arsenic and cardiovascular morbidity and mortality. The only prospective cohort study, published recently by Moon *et al* [140] reported that long-term exposure to low to moderate arsenic levels is associated with CVD incidence and cardiovascular mortality. Participants of this study had a median urinary arsenic level of 9.7 μg/g creatinine, with a range from 1 to 183.4 μg/g creatinine and

1.71 (95% CI 1.19-2.44, P <.001 for trend), and 3.03 (95% CI 1.08-8.50, P <.001 for trend), respectively. The association of arsenic with CVD mortality was stronger in participants with diabetes. Evidence is also

accumulating on the association between higher levels of arsenic exposure and cardiovascular morbidity and mortality in Bangladesh [141]. High levels of well-water arsenic exposure are recognized as being causative in the development of PAD [142-144], such as Blackfoot disease. This is a severe form of PAD endemic to Taiwan characterized by thromboangiitis obliterans, severe arteriosclerosis, and high levels of vessel wall arsenic [142-144]. However, the generalizability of these findings is limited, due to the nature of the exposure (deep well water) and the extremely high estimated levels of arsenic exposure. Finally, although the literature is limited, there is evidence to suggest a positive relationship between arsenic exposure and hypertension [145].

6. The Metabolic Effects of Heavy Metals

The knowledge gained about the homeostasis of heavy metals has been substantial over more than a decade [51]. Although they have no known metabolic function, when present in the body they disrupt normal cellular processes, leading to toxicity in a number of organs [51]. They are relatively poorly absorbed into the body, but once absorbed are slowly excreted and accumulate in the body causing organ damage. Thus, their toxicity is in large part due to their accumulation in biological tissues, including food animals such as fish and cattle as well as humans. Distribution of heavy metals in the body relies on its binding to carrier molecules in the circulation. Metallothioneins are small proteins rich in cysteine residues, which accounts for the unique metal binding properties of metallothioneins and play a major role in the dispersal and storage of heavy metals in the body. They also accumulate in hair and toenails (e.g., arsenic and mercury), which both can be used as indicators of long-term exposure in population studies. These heavy metals have a slow excretion rate from the body, as indicated by their long half-life time (e.g., half-life of lead is 27 year in cortical bone and 16 year in cancellous bone, half-life of cadmium is 10–30years), compared with their uptake rate. Several international bodies, like the Center of Disease Control (CDC), World Health Organization (WHO), Occupational Safety and Health Administration (WHO-OSHA), have made evaluations of heavy metals toxicity International Programme on Chemical Safety (WHO-IPCS), Joint FAO/WHO Expert Committee on Food Additives (JECFA), and International Agency for Research on Cancer (IARC) (Table 1) [51].

6.1. *Hypothetical mechanisms of metal toxicity*

Heavy metals are toxic because they may have cumulative deleterious effects that can cause chronic degenerative changes [150], especially to the nervous system, liver, and kidneys, and, in some cases, they also have teratogenic and carcinogenic effects [151]. The mechanism of toxicity of some heavy metals remains unknown, although enzymatic inhibition, impaired antioxidants metabolism, and oxidative stress may play a role. Heavy metals generate many of their adverse health effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, and depletion of protein sulfhydryls (e.g., glutathione) [152]. The importance of these metals as environmental health hazards is readily evident from the fact that they ranked in the top 10 on the current Agency for Toxic Substances and Disease Registry Priority List of Hazardous Substances [153]. This listing is based on the toxicity of the substance and the potential for exposure from air, water, or soil contamination. Because of the extensive use of these metals and their compounds in industry and consumer products, these agents have been widely disseminated

in the environment. Because metals are not biodegradable, they can persist in the environment and produce a variety of adverse effects. Maximum levels for heavy metals in food have been set in consideration for possible chemical contaminants. Table 2 [51], represents classification of CVD risk factors.

Table 1. Non-cardiovascular harmful effects of heavy metals.

Heavy metal	Most affected organs	Chronic health effects	References
Arsenic	(i) Central nervous system (ii) Lungs (iii) Digestive tract (iv) Circulatory system (v) Kidneys	(i) Cancers. (ii) Peripheral vascular disease, which in its extreme form leads to gangrenous changes (black foot disease, only reported in Taiwan). (iii) Skin lesions (melanosis, keratosis). (iv) Hearing loss. (v) Reproductive toxicity. (vi) Hematologic disorders. (vii) Neurological diseases. (viii) Developmental abnormalities and neurobehavioral disorders.	[146]
Lead	(i) Central nervous system (ii) Erythropoiesis (iii) Kidneys (iv) Liver	(i) Cancers (ii) Kidney damage (iii) Neurological diseases (iv) Impaired intellectual ability and behavioral problems in children	[147]
Cadmium	(i) Kidneys (ii) Bone (iii) Liver (iv) Lungs	(i) Cancers (ii) Kidney damage (iii) Bronchiolitis, COPD, emphysema, fibrosis (iv) Skeletal damage, first reported from Japan, the itai-itai (ouch-ouch) disease (a combination of osteomalacia and osteoporosis)	[148]
Mercury	(i) Central nervous system (ii) Kidneys (iii) Liver (iv) Lungs	(i) Lung damage (ii) Kidney damage (iii) Neurological diseases (iv) Impaired intellectual ability and behavioral problems in children (v) Metallic mercury is an allergen, which may cause contact eczema (vi) Mercury from amalgam fillings may give rise to oral lichen	[149]

Table 2. Classification of CVD risk factors.

Category	Examples	References
Non-modifiable risk factors	(i) Advancing age (ii) Male gender (iii) Family history/genotype	(i) [154] (ii) [155] (iii) [156]
Metabolic risk factors	(i) Hypertension (ii) Diabetes mellitus/glucose intolerance (iii) Metabolic syndrome (iv) Hyperlipidemias (v) Obesity/overweight	(i) [157] (ii) [158] (iii) [159] (iv) [160] (v) [161]
Lifestyle risk factors	(i) Smoking (ii) Physical activity (iii) Diet	(i) [162] (ii) [163] (iii) [164,165]
Novel risk factors	(i) Lipoprotein (a) (ii) Homocysteine (iii) Inflammatory markers (e.g., C-reactive protein) (iv) Prothrombotic factors (e.g., fibrinogen) (v) Trace elements (e.g., selenium, zinc, copper, chromium) (vi) Heavy metals (e.g., arsenic, lead, cadmium, mercury)	(i) [166] (ii) [167] (iii) [168-171] (iv) [113,172-174]

The association of environmental pollutants, including metals, with cardiovascular disease has been reviewed elsewhere [111, 175]. In this review, we will summarize the evidence for the metals that are chelated most effectively by edentate disodium and that have convincing published reports documenting their cardiovascular toxicity: lead and cadmium, ranked second and seventh, respectively, as environmental chemicals of concern by the Agency for Toxic Substances and Disease Registry [176]. There are general mechanisms that apply to all toxic metals and specific mechanisms that are idiosyncratic to the individual metal in question. These mechanisms center on oxidative stress. Although the science underlying these mechanisms is accurately quoted, attribution of benefit to metal chelation because of these mechanisms has to be considered speculative. Moreover, the oxidative-stress = oxidative-damage hypothesis has been challenged as well. Oxidative stress results from an imbalance between the production and detoxification of reactive oxygen species (ROS). The toxicity of ROS is based on their ability to oxidize intracellular and extracellular structures such as proteins, lipids, and nucleic acids (Figure 3). Several enzyme systems are known to protect the body against ROS. These enzymes include superoxide dismutase, catalase, glutathione peroxidase, paraoxonase, thioredoxin, heme oxygenase, and others. Glutathione peroxidase is of particular interest. Many metals have electron-sharing properties and, therefore, are capable of forming covalent bonds with sulfhydryl groups of proteins (eg, glutathione, cystein, homocysteine, metallothionein, and albumin) [177]. By binding to glutathione, these metals deplete its levels and, therefore, increase the intracellular concentration of ROS. The consequences include promotion of lipid peroxidation; cell membrane damage; DNA damage; oxidation of aminoacids in proteins and, therefore, changes in their conformation and function; and inactivation of enzymes. According to current concepts of atherogenesis, oxidative modification of LDL, a free radical-driven lipid

peroxidation process, is an early event in atherosclerosis development [178]. Many metals have been shown to increase lipid peroxidation [179, 180].

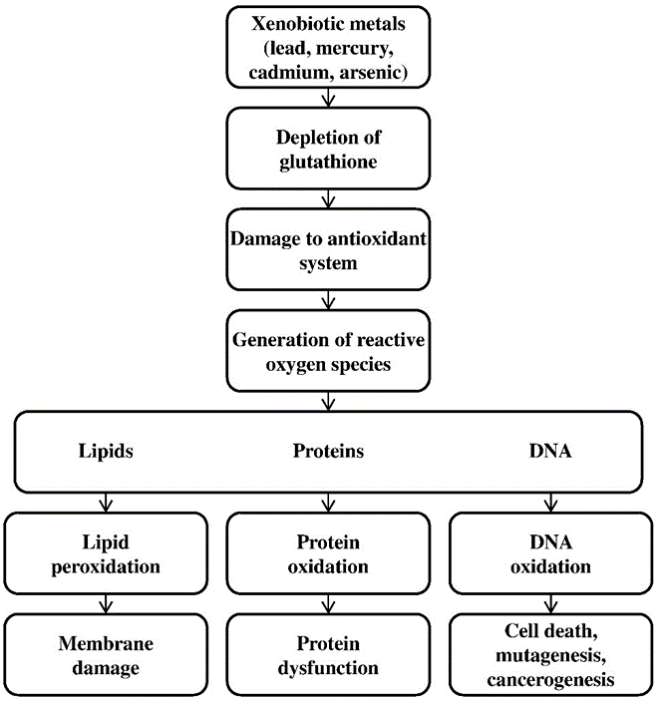

Figure 3. Hypothetical Mechanisms of Metal Toxicity.

In addition, metal-related, ROS-mediated changes include microtubule destruction, mitochondrial damage by disruption of the membrane potential, inhibition of adenosine triphosphate production, followed by dysfunction of ion transporters such as Ca–adenosine triphosphates and Na–K–adenosine triphosphate causing changes in calcium homeostasis [181]. By binding to sulfhydryl groups of proteins not involved in the detoxification of ROS, metals may cause other biological impairments. Lead causes endothelial dysfunction by binding and inhibiting endothelial nitric oxide synthase and decreasing nitric oxide production [182, 183]. Mercury has also been reported to impair nitric oxide metabolism by binding to sulfhydryl (SH) groups of NF-kB and changing its effects on gene expression and, thus, resulting in decreased expression of inducible nitric oxide synthase[184]. Food-like fish has been implicated in the alteration of mercury metabolism. In terms of macronutrient intakes such as fat intake, a positive correlation between dietary mercury and low-density lipoprotein cholesterol levels was observed[185].Unsaturated fatty acids were also correlated with mercury exposure in populations frequently consuming seafood and fish [186]. Studies on the effects of macronutrients on mercury metabolism are expected to shed some light on possible interactions between different nutrients as they have been shown to modulate toxicokinetics and dynamics of mercury metabolism [187]. As in the limited understanding of the mechanisms of mercury toxicity [188], nutritional consideration may often be concurrent with or may be additive to genetic predisposition to mercury exposure [189]. However, more focus was attributed to mercury retention by various organs in efforts to explain nutrient mercury interactions [190]. Environmentally induced changes in gene regulatory mechanisms along with dietary interactions may exacerbate mercury intoxication. Metallothionein protein, rich in sulfhydryl groups, helps in scavenging and reducing the toxic effects of mercury. Metallothionein induction is not only seen with mercury but various other metals like cadmium, zinc, and copper [191]. Toxic effects of mercury also induce a number of stress proteins, which include heat shock proteins and glucose-regulated proteins that have also been implicated in cardiovascular pathophysiology [192]. Cadmium has been shown to inhibit endothelial and calcium-calmodulin constitutive nitric oxide synthase as well [193]. Arsenic exposure was linkedto impairment of nitric oxide production and increase dgeneration of ROS, perhaps by uncoupling of endothelial nitric oxide synthase production [194].

There are additional, idiosyncratic mechanisms of toxicity. Thus, lead, competing with zinc, binds to sulfhydrylgroups of delta-aminolevulinic acid dehydratase (theenzyme involved in heme metabolism), preventing binding of delta-aminolevulinic acid dehydratase to amino levulinicacid, [195] generating ROS [196]. Lead has also been shown to promote endothelial release of endothelin, to elevate serum levels of nor-epinephrine, angiotensin-converting enzyme and thromboxane and to decrease production of prostacyclin [197-198]. All these changes may mediate vascular constriction. In addition, lead, being one of the calcium-like elements, competes with calcium for transport by channels and pumps in endoplasmic reticulum. Lead may also substitute for calcium in calcium-dependent processes and can interact with calmodulin. Arsenic inhibits pyruvate and α-ketoglutarate dehydrogenases, important enzymes of gluconeogenesis andglycolysis [198]. It can also replace phosphate in glycolysis, generating arseno-3-phosphoglycerate instead of 1,3-bisphosphoglycerate, which leads to uncoupling of oxidative phosphorylation [199]. Moreover, arsenic has been linked to increased intravascular inflammation by up-regulating interleukin 6; tumor necrosis factor α; and monocyte chemotactic protein, vascular cell adhesion molecule and intercellular adhesion molecule [200]. Furthermore, arsenic inhibits expression of peroxisome proliferator–activated receptor γ causing hyperglycemia and dyslipidemia [201].

Macrophages and endothelial cells take up cadmium by endocytosis causing foam cell production followed by foam cell necrosis and endothelial cell disruption followed by endothelial cell necrosis. Once the endothelial layer is disrupted, cadmium reaches smooth muscle cells and accumulates there, activating smooth muscle cell proliferation and apoptosis. Cadmium may also substitute for iron and copper in proteins those contain these biologically necessary metals. As a result, iron and copper, after being released from its usual binding proteins, may produce ROS, as both elements can be more easily involved in reduction-oxidation reactions [124]. Cadmium is also associated with perturbations in inflammation and coagulation, including elevated blood C-reactive protein and fibrinogen in a general US population, even after adjustment for other CVD risk factors such as smoking [200, 202-203]. Moreover, cadmium exposure has been associated with elevations of mediators or markers of systemic inflammation, including interleukin 6, tumor necrosis factor α, and vascular cell adhesion molecule 1 [204].

7. Standard Therapies

Specific differences in the toxicities of heavy metal ions may be related to differences in solubility's, absorbability, transport, chemical reactivity and the complexes that are formed within the body. Chelation is the basis of much of the physiology of multivalent cations and of the toxicokinetics and toxicodynamics of heavy metals.

7.1. *EDTA Chelation vs. Conventional Therapy for Vascular Disease*

EDTA chelation may be one of the most effective, least expensive, and safest treatments for heart disease [205] ever developed, yet it is practiced by perhaps only 2,000 physicians in the United States. It saves far more lives than conventional treatments for heart disease and other chronic degenerative diseases at a fraction of the cost. EDTA chelation is a therapy [205] by which repeated administrations of a weak synthetic amino acid (EDTA, ethylenediamine tetra-acetic acid) gradually reduce atherosclerotic plaque

and other mineral deposits throughout the cardiovascular system by literally dissolving them away. EDTA normalizes the distribution of most metallic elements in the body. Alternative practitioners have long used EDTA chelation [205-206] therapy to treat heavy metal toxicity, with great success .EDTA is a cheap, safe chemical that binds metals, and is in fact used as a food preservative, since it binds calcium and other heavy metals, preventing oxidation and bacterial growth. EDTA is given intravenously, it binds to heavy metals in the body, and the EDTA-metal complex is then excreted. A new study recently appeared that found positive results for EDTA chelation therapy: Heavy Metals, Cardiovascular Disease, and the Unexpected Benefits of Chelation Therapy [15]. EDTA chelation therapy is commonly used for reducing cardiovascular events in people with previous cardiovascular disease [206]. Chelation therapy with EDTA [15, 18] (edetate disodium) has been used to treat atherosclerotic disease since 1956[207]without a solid scientific base. In 2002, the Cochrane Collaborative [208] reported that there was insufficient evidence to make a recommendation for or against chelation therapy. Yet patients continued to seek, and practitioners to use, EDTA to prevent or treat atherosclerotic disease of the coronaries, carotids, and peripheral arteries. In 2002, Trial to Assess Chelation Therapy (TACT), a 2 × 2 factorial trial testing 40 disodium EDTA infusions versus placebo and oral high dose multivitamins and minerals versus oral placebo was designed [209] and funded. TACT enrolled 1,708 patients [210] who had sustained a prior myocardial infarction, were at least 50 years old, and had a creatinine of ≤ 2.0mg/dL. TACT administered 55,222 infusions of EDTA-based chelation or placebo. EDTA chelation significantly reduced, by 18% (p= 0.035), a combined cardiovascular endpoint, with a 5-year number needed to treat of 18. In 633 patients who had diabetes,97 a diagnosis associated with a strong pro oxidant state, the reduction in events was greater, with a 41%reduction in events and a number needed to treat of 6.5patients over 5 years (unadjusted P = .0002). Thus TACT provides a strong inferential support for the conclusion that environmental metal pollution may be a potent and modifiable risk factor for atherosclerotic disease. The main treatment of heavy metal poisoning is termination of exposure to the metal. Treatment also consists of the use of various chelating agents that cause the toxic (poison) element to bind with the drug and be excreted in the urine. Three common drugs for treatment of metal poisoning are: BA (Dimercaprol), Calcium EDTA (Calcium Disodium Versenate) and Penicillamine. Each of these works by binding actions that permit the metals to be eliminated from the body through the urine.

Although the treatment regimens tested in TACT were complex, the most reasonable presumption is that edetate disodium was the primary active therapeutic agent responsible for the results. To investigate the chelating effect of edetate disodium, Waters *et al* [211] collected 24 h urines for 2 days before and 2 days after an edetate disodium–based infusion similar to that used in TACT and analyzed the samples for various toxic and essential metals. Following the infusion, the excretion of lead over 2 days increased by 3,830% and of cadmium by 514%. A similar experiment performed by Arenas *et al* [212] demonstrated similar results, but in this case with the identical TACT solution in TACT-eligible patients. Compared with baseline, a single infusion increased lead excretion by 3,887% and cadmium by 670%. These findings raise the possibility that edetate disodium mobilizes lead and cadmium from their

chronic tissue storage compartments and facilitates their excretion. In our review, we focus on cadmium and lead because those are the metals with the strongest epidemiological and experimental evidence in support of a role in cardiovascular disease development.

7.2. *Oxidative stress and seasonality*

Bivalves are able to survive in a wide range of oxygen concentrations ranging from anoxic to high levels of dissolved oxygen. Variations in this ability have been proposed as an index of environmental stress [213]. Oxyradicals (O^{-}_{2}, H_2O_2, ·OH) can be highly toxic to aquatic organisms often resulting in lipid peroxidation in membranes, altered pyridine nucleotide redox status and DNA damage [214]. Moreover, many xenobiotics are capable of modulating oxidative stress either by acting directly as redox cycling compounds (e.g. menadione) or as a consequence of biotransformation to quinones which are redox cycling (e.g. benzo(*a*)pyrene) [215]. A range of antioxidant defense mechanisms are present in bivalve mollusks. These enzyme activities (catalase, superoxide dismutase, GSH peroxidase) and antioxidant compounds (e.g. vitamin E and GSH) are known to be under extensive seasonal control. In digestive gland, levels of these antioxidant activities and molecules appear to be at their lowest in winter (November–March), corresponding to increases in levels of lipid peroxidation products, a useful index of oxidative stress[216].Hence application of an external source of antioxidants [47] may offer some protection against oxidative stress. The term antioxidant refers to a wide spectrum of compounds, which are able to donate electrons and neutralize free radicals, resulting in the prevention of cell injuries [217,218]. In consequence, the search for effective, nontoxic, natural compounds with antioxidant activity has been intensified in recent years [219-221]. In particular, curcumin (a dietary spice isolated from Curcuma longa) has become one of the most cited antioxidants due to the multitude of beneficial health effects that have been studied and established by the scientific community [222]. However, there is little information about the protective effects of curcumin against noxious effects caused by exposure to heavy metals in murine models, including those related to hepatic damage.

7.3. *Curcumin*

Curcumin or diferuloylmethane (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is a hydrophobic polyphenol compound naturally concentrated in the rhizome of the herb *Curcuma longa*, commonly known as turmeric [223]. Traditionally, turmeric has been used in therapeutic preparations against biliary disorders, anorexia, coryza, herpeszoster, acne, cough, urinary tract diseases, diabetic wounds, hepatic disorder, rheumatism and sinusitis [224-226]. At present, turmeric is used as a dietary spice, and by the food industry as additive, flavoring, preservative and as coloring agent in foods and textiles [227-229]. Curcumin is a major component of turmeric andit has been shown to exhibit several activities including antioxidant [230-233], antimicrobial [234,235], anti-inflammatory [236, 237], antiviral [238, 239] and anti-carcinogenic [240-245].

Curcumin and turmeric products have been characterized as safe by the Food and Drug Administration (FDA) in the USA, the Natural Health Products Directorate of Canada and the Joint FAO/ WHO Expert Committee on Food Additives of the Food and Agriculture Organization/World Health Organization [246]. Over 2400 metric tons of turmeric is imported into the USA [247]. Curcumin chelates heavy metals, and successfully prevented lead and

cadmium induced lipid and brain damage in rats [248].Daily use of curcumin, at 500 to 1500 mg a day, could therefore be expected to remove toxic heavy metals from the body and prevent tissue damage. And in fact, curcumin has anti-atherosclerotic activity [249].

7.3.1. *Therapeutic potential*

Curcumin chelates heavy metals, and successfully prevented lead and cadmium induced lipid and brain damage in rats [248,249]. Daily use of curcumin, at 500 to 1500 mg a day, could therefore be expected to remove toxic heavy metals from the body and prevent tissue damage. And in fact, curcumin has anti-atherosclerotic activity [249].

Despite its low bioavailability, numerous clinical studies have suggested that curcumin has therapeutic efficacy against various human diseases [250], including cancer [251-252], diabetes [253], Alzheimer's disease [254], familial adenomatous polyposis [255], inflammatory bowel disease [256], rheumatoid arthritis [257, 258], hypercholesterolemia [259] and liver injury [260], atopic asthma [261], psoriasis [262], osteoarthritis [263], neurological diseases [264], chronic anterior uveitis [265, 266], human immunodeficiency virus infection [267] and cystic fibrosis [268].Enhancing curcumin's bioavailability in the near future is will enable this promising natural product to be investigated as a therapeutic agent for treatment of human disease [269].

7.3.2. *Antioxidant properties*

Curcumin is a bis-α,β-unsaturated β-diketone and the β-diketo moiety undergoes keto-enol tautomerism (Figure 4). Under acidic and neutral conditions, the bis-keto form predominates, whereas the enol form is found above pH 8. The enol form makes an ideal chelator of positively charged metals (Figure 5), which are often found in the active sites of target proteins [270].

Figure 4. Curcumin keto-enol tautomerism. The presence of the phenolic, b-diketone, as well as the methoxy groups contributes to the free-radical-scavenging activity of curcumin. The enol form makes an ideal chelator of positively charged metals. While the presence of keto-enol functionality and the aromatic ring system must be present to provide Nrf2 inducer activity to curcumin.

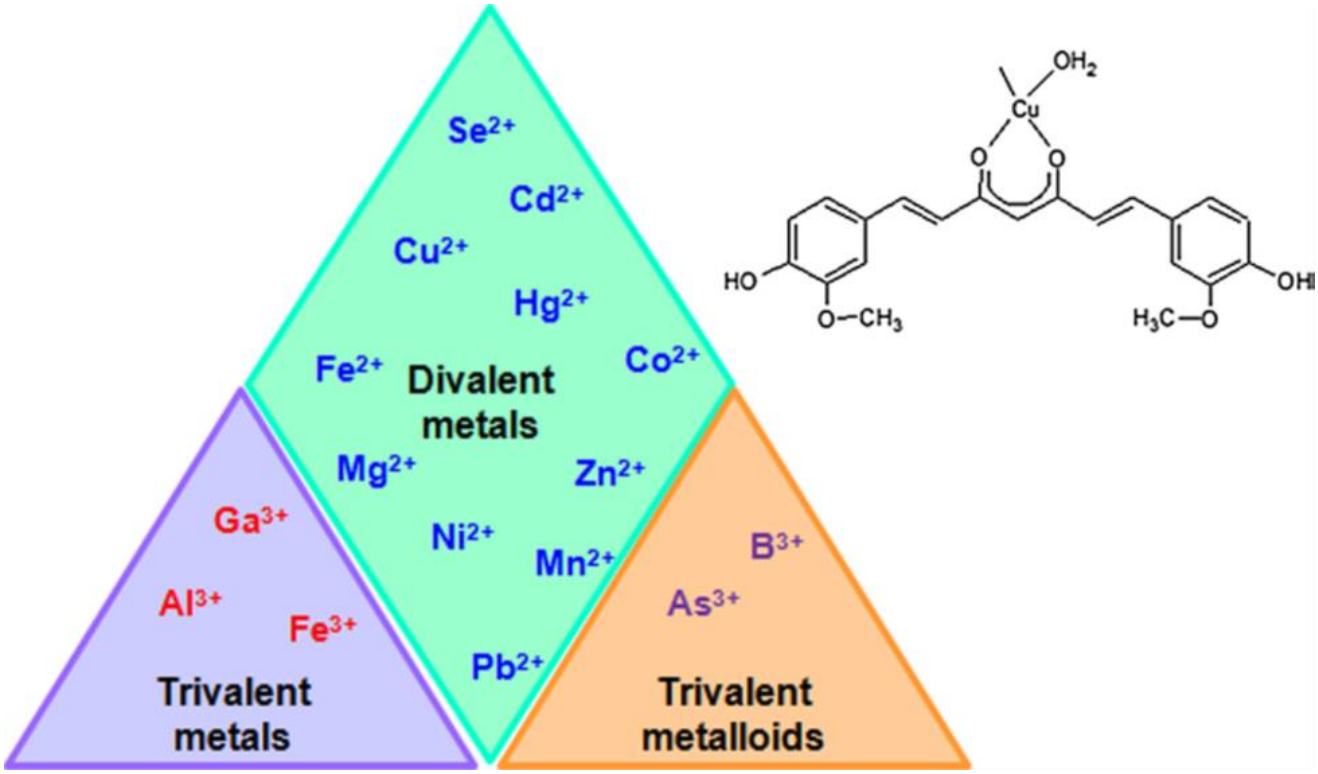

Figure 5. Curcumin chelating potential for metallic and semi metalic cations.

Curcumin chelating potential of the type 1:1 and 1:2 have been reported for several metal cations [271].

The presence of the phenolic, β-diketone, as well as the methoxy groups contribute to the free-radical-scavenging activity of curcumin [272]. Curcumin has demonstrated scavenging activity against a variety of ROS, including $O_2^{\cdot-}$, $HO^{\cdot}$, peroxyl radical ($ROO^{\cdot}$), nitrogen dioxideradical ($NO_2^{\cdot}$), 1,1-diphenyl-2-picryl-hydrazyl free radical ($DPPH^{\cdot}$),2,20-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) and N,N-dimethyl-p-phenylenediamine dihydrochloride ($DMPD^{\cdot+}$) radical[273-276]. On the other hand, curcumin may protect cells from oxidative stress indirectly by inducing Nrf2 (Figure 6) [220, 277-279].

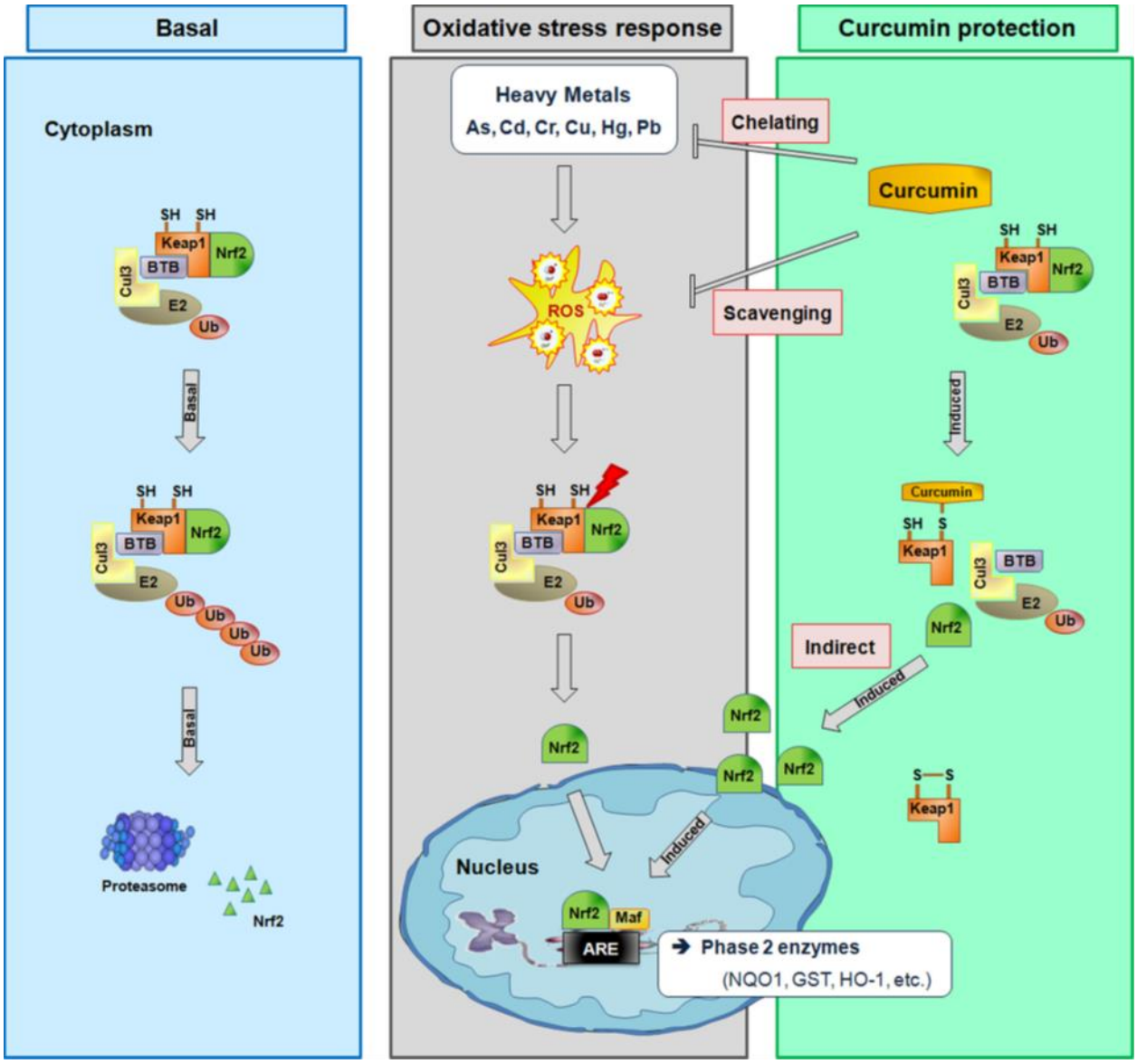

Figure 6. General scheme for the induction of gene expression through Keap1/Nrf2/ARE pathway. Nrf2 is a redox-sensitive transcription factor, which, under basal conditions, is bound to its repressor Keap1 in the cytoplasm. Keap1 serves as an adaptor protein between Nrf2 and the Cul3 complex, leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome. Oxidative stress induced by heavy metals exposure leads to the activation of the Nrf2/Keap1/ARE pathway. Protective effects of curcumin were attributed to its ability to scavenge free radicals, to act as a chelating agent and/or its capacity to induce detoxifying enzymes by the up regulation of Keap1/Nrf2/ARE pathway. Reactive oxygen species (ROS), Kelch-like ECH-associated protein 1 (Keap1); nuclear factor (erythroid-derived 2)-like 2 (Nrf2); antioxidant responsive element (ARE); cullin-3 (Cul3); NADPH: quinone oxidoreductase 1 (NQO1); glutathione-S-transferase (GST); heme oxygenase-1 (HO-1).

Nrf2 belongs to the CNC (cap 'n' collar) family of b-Zip transcription factors, together with p45 NF-E2, Nrf1 and Nrf3, and acts through the formation of a hetero dimer with one of the small Maf proteins [280-281]. Nrf2 is a redox-sensitive transcription factor, which, under basal conditions, is bound to its repressor Keap1 in the cytoplasm [282-285]. Keap1 serves as anadaptor protein between Nrf2 and the Cullin3-based E3-ligaseubiquitylation complex, with its N-terminal BTB leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome [286, 287]. Curcumin contains two Michael reaction acceptor functionalities in its molecule that can modify the cysteine residues of Keap1 and promote a conformational change in the Nrf2-Keap1 complex by Michael addition to the thiols in Keap1 [288, 289], thereby releasing Nrf2 and allowing it to translocate into the nucleus and bind as a hetero dimer to ARE in DNA to initiate target gene expression and increase the expression of phase II enzymes [290-292]. Dinkova-Kostova and Talalay, 1999 [290] identified that the presence of keto-enol functionality and the aromatic ring system to provide an Nrf2 inducer activity to curcumin. In this way, curcumin up-regulates genes that contain AREs in their promoters, including superoxide dismutase (SOD), catalase (CAT) [293], glutathione peroxidase (GPx) [294], glutathione reductase (GR), glutathione-S-transferase (GST) [295], heme oxygenase 1 (HO-1) [289], NADPH:quinone oxidoreductase 1 (NQO1), glutamate cysteine ligase catalytic (GCLC) and regulatory (GCLM) subunits [296] and aldose reductase [297]. Curcumin natural analogues from turmeric, other naturally occurring analogues, synthetic analogues, and curcumin formulations exhibit different antioxidant activities in several *in vitro* and *in vivo* models [298]. Curcumin was more potent than demethoxycurcumin and bisdemethoxycurcumin [299-300]. However tetrahydro curcumin, one of the major metabolites of curcumin, exhibits greater antioxidant potential than curcumin in most models [301-302]. On the other hand, the information about the antioxidant potential of curcumin in comparison with other naturally-occurring analogues is scarce; as a result, it is necessary to perform comparative studies about it. In this respect, caffeic acid, ferulic acid and capsaicin have shown a higher relative antioxidant potency than curcumin, but not eugenol or dehydrozyngerone in some models [303-305], indicating that an ortho-methoxylated phenolic chromophore is necessary for antioxidant activity. Finally, molecular design and synthesis of synthetic curcumin analogues have improved the antioxidant activity in contrast with curcumin in many experimental conditions [306-308]. Finally, Curcumin reduces the hepatotoxicity induced by arsenic, cadmium, chromium, copper, lead and mercury, prevents histological injury, lipid peroxidation and glutathione (GSH) depletion, maintains the liver antioxidant enzyme status and protects against mitochondrial dysfunction. The preventive effect of curcumin on the noxious effects induced by heavy metals has been attributed to its scavenging and chelating properties, and/or to the ability to induce the Nrf2/Keap1/ARE pathway. However, additional research is needed in order to propose curcumin as a potential protective agent against liver and heart damage induced by heavy metals. Green tea extract also protects against cadmium toxicity [309]. What may be going on is that GTE increases glutathione, which in turn removes the metals. N-acetylcysteine is another OTC supplement that has metal-chelating effects [310]. So, we see that in addition to EDTA

chelation therapy, a number of other supplements can chelate heavy metals. These could all be used for prevention.

However, the exact mechanism of CVD induced by heavy metals deserves further investigation through new technologies such as nanotechnology [311-316]. Nanotechnology is a major innovative scientific and economic growth area, which may present a variety of hazards for environmental and human health.

8. Conclusion

There is strong evidence that xenobiotic heavy metals contamination is linked to atherosclerotic disease and is a modifiable risk factor. Because of their high degree of toxicity, xenobiotic heavy metals, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals that are of public health significance. The combination of a susceptible genetic background and dietary heavy metals along with environmental co-exposure to xenobiotic metals may explain some aspects of their cardiovascular disease CVD. Accumulation of biologically active heavy metals is an important risk factor for cardiovascular disease. Toxic xenobiotic heavy metals are resulting in the production of reactive oxygen species as superoxide ion, hydrogen peroxide, and hydroxyl radical (O^{-}_{2}, H_2O_2, $^{\cdot}OH$). Consequently, enhanced lipid peroxidation, DNA damage, and altered calcium and sulfhydryl homeostasis occur. Fenton-like reactions may be commonly associated with most membranous fractions including mitochondria, microsomes, and peroxisomes. Mechanisms associated with the toxicities of metal ions are very similar to the effects produced by many organic xenobiotic. Mainstream medicine should consider treating atherosclerosis and CVD by using EDTA chelation therapy. Edentate's chelation therapy is a cheap, safe chemical that binds metals, and is in fact used as a food preservative, since it binds metals, preventing oxidation and bacterial growth and reducing CVD. Curcumin reduces the hepatotoxicity induced by arsenic, cadmium, chromium, copper, lead and mercury. The preventive effect of curcumin on the noxious effects induced by heavy metals has been attributed to its scavenging and chelating properties, and/or to the ability to induce the Nrf2/Keap1/ARE pathway.

9. Conflict of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

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NA

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