Lead as an environmental cardiovascular risk factor

INTRODUCTION

From ancient civilizations to modern technocratic society, human health has been a burning issue that troubled all people. In 300 BC, the Greek anatomist and surgeon Herophilus of Chalcedon wrote: “To lose one’s health renders science null, art inglorious, strength unavailing, wealth useless, and eloquence powerless.” In a poll conducted by the Gallup Institute in 1999 among 50000 individuals from 60 different countries, the majority of respondents chose good health as the most valued entity among such categories as job, education, freedom, good health, happy family, etc.

Cardiovascular diseases (CVD) are diseases and injuries of the cardiovascular system: the heart, the blood vessels of the heart, and the system of blood vessels throughout the body and within the brain. CVD are the leading cause of deaths (1). In 2003, CVD killed 16.7 million people worldwide, which constitutes 29.2% of total deaths according to the World Health Report. Interestingly, CVD became the leading cause of death in developed countries from the middle of the 20th century, and since 2001 they have become the leading cause of death in the developing world (2, 3). Nearly half of all deaths in developed countries and approximately 28% of deaths in low- and middle-income (developing) countries are the result of CVD (3). Thirty-six per cent of deaths in North America are due to CVD, whereas in Europe CVD cause over 4.35 million deaths annually, i.e. 49% of all deaths. Epidemical character of heart disease and stroke is reflected in increase in personal, community and health care costs. In Canada, CVD is the underlying cause of death for one in three Canadians. Eight in ten Canadians have at least one risk factor for CVD and 11% have three risk factors or more (4). CVD have the largest economic impact of all illnesses in Canada. In 1998, Health Canada estimated the total cost to the health sector and the Canadian economy to be approximately 18.5 billion dollars (5).

ENVIRONMENTAL CARDIAC RISK FACTORS

About sixty years ago, Framingham Heart Study first identified three key cardiac risk factors: high blood pressure, high cholesterol and smoking. Before that, it was generally thought that heart attacks come out of nowhere without any apparent reason. Even high blood pressure was considered as a part of the normal aging process. Later, three more risk factors, such as physical inactivity, obesity, and diabetes were recognized as major cardiovascular risk factors. Although cardiovascular risk factors most often appear in clusters, there are data indicating that hypertension is present in over 85% of patients who develop heart failure (6).

Environmental factors are also considered as key determinants of CVD (7). Initially, a significance of environmental factors in CVD was
demonstrated in the Seven Countries Study started in 1958 on three continents, North America, Europe, and Asia (8). The Study detected up to five-fold differences in prevalence, incidence of and mortality from CVD among populations with various geographic, ethnic, and cultural characteristics. The above features would be approximately equal, if only normal aging was a factor. Higher incidence rates were found in North America and northern Europe comparing to southern Europe and Japan.

The incidence of CVD is also not evenly distributed in the USA according to the findings published in 2007 by the Center for Disease Control and Prevention, Atlanta, GA (9). Based on telephone interview of 350000 participants throughout the USA, the report showed that West Virginia, Puerto Rico, and Kentucky have the highest proportion of residents with heart disease, whereas Hawaii, Colorado, and the US Virgin Island have the lowest.

Although lifestyle choices such as smoking, diet, and exercise are viewed as major environmental factors, there is accumulating evidence suggesting that exposure to pollutants and chemicals could elevate the risk of CVD. For example, postmenopausal women in the USA, regardless of any risk factors for cardiovascular disease, were found to be at increasing risk of fatal and non-fatal cardiovascular events with greater long-term exposure to the fine particulate air pollution, PM2.5, i.e., airborne particles < 2.5 μm in diameter (10). It was shown that there was a 24% increase in any CV event, 76% jump in CV mortality, and more than double increase in mortality from any later diagnosed coronary heart disease for every 10 μg/m³ rise in particulate air-pollution concentrations. Interestingly, such level of PM2.5 pollution is not unusual. As a matter of fact, the levels of PM2.5 exposure in the USA in 2000, varied from the lowest 3.4 (observed in Honolulu) to the highest 28.3 (Riverside, California) with the mean of 13.5 μg/m³, and the National Ambient Air Quality Standard required by the Clean Air Act of the USA is 15 μg/m³ PM2.5 (11).

The study of 4494 adults aged 45 to 74 years showed that living near busy roads increases incidents of coronary atherosclerosis (12). Recently, first evidence of causal link between brief exposure to diesel fumes during physical exercise and myocardial infarction has been obtained (13).

Above mentioned outcomes have only recently been observed and the correlation between human exposure to environmental chemical pollution and cardiovascular events remains to be investigated in more details. More than 80000 chemicals are currently registered in the United States for commercial use, and the influence on CVD of only few of them has been examined (7). The increasing use of nanomaterials is another area of emerging concern (14). Exposures to arsenic, lead, cadmium, pollutant gases, solvents, and pesticides have been linked to increased incidence of CVD (7, 15). The death rates for certain types of CVD have been found to be higher in soft water areas than in hard water areas in many parts of the world (15, 16, 17, 18). It is thought that at lower concentration of calcium and magnesium, which are essential elements determining most water hardness, heavy metal ions, e.g. lead, are better absorbed by humans. A significant protective effect of calcium intake from drinking water on the risk of death from acute myocardial infarction has been shown (19). An association between dementia (including Alzheimer’s disease) and high concentrations of aluminum in drinking water is suggested especially for the most elderly (20). Also, an unusually high incidence of Lou Gehrig’s and Parkinson’s diseases in indigenous populations in Guam and New Guinea suggests a possible correlation between the diseases and local environmental conditions, including high levels of aluminum and low levels of calcium and magnesium in soil and food (20).

In this perspective, I will briefly review pathophysiological effects of lead exposure with emphasis on cardiovascular system and the major sources of human exposure to environmental lead.

**CARDIOTOXIC AND OTHER PATHOPHYSIOLOGICAL EFFECTS OF LEAD**

Lead occurs naturally in the environment and has many industrial uses. However, even small amounts of lead can be hazardous to human health. One gram of lead in 20000 liters of water makes it unfit for drinking. In extreme cases, short-term exposure to high levels of lead can cause vomiting, diarrhea, paralysis, convulsive seizures, coma or even death (21). Acute lead poisoning causes various symptoms related to the nervous system: headache, irritability, abdominal pain, sleeplessness, restlessness; children may be affected by behavioral disturbances, learning and concentration difficulties. In severe cases, the affected person may suffer from acute psychosis, confusion and reduced consciousness (22). Symptoms of long-term exposure to lower lead levels may be less noticeable but are still serious.

Association between lead exposure and CVD in human population was recently reviewed by Navas-Acien et al. (23). In several clinical trials and population studies, occupational exposure to lead was shown to correlate with increased incidence of hypertension, cerebrovascular and cardiovascular disease (24, 25). Cardiotoxic effects of lead, for which positive association with lead exposure has been suggested, are as follows. Lead causes peripheral arterial occlusive disease and, possibly, direct myocardial injury. Lead poisoning is associated with myocarditis and sinus bradycardia. EKG abnormalities are reported for children and lead-exposed workers. Lead promotes hydroxyl radical generation and lipid peroxidation in cultured aortic endothelial cells and may induce the procoagulant activity of blood cells directly leading to thrombosis. Lead affects both human erythrocytes and lymphocytes (26). In erythrocytes, it could degenerate the lipid and protein components and suppress hemoglobin synthesis.

Besides cardiovascular outcomes, lead has detrimental effects on the central nervous, gastrointestinal, repro-
ductive, renal and immune systems (22). In the brain, lead has toxic effects on neurons, vascular endothelial cells, astroglia, and oligodendroglia. It induces apoptosis and excitotoxicity, as well as disturbances in the storage and release of neurotransmitters and second messengers. Long-term exposure to lead causes memory deterioration, prolonged reaction time and reduced ability to understand. It reduces nerve conduction velocity and dermal sensitivity. Lead exposure diminishes intellectual capacity in children. For every 10 μg/dL increase in blood lead, IQ decreases by 2 points (27). Notably, the mean IQ in the USA is 100 and people with IQ less than 70 are considered to be mildly mentally retarded.

Chronic inorganic lead toxicity results in growth retardation, intellectual impairment, and hyperactivity (21). Developmental exposure to lead upregulates the expression level of amyloid precursor protein involved in Alzheimer’s disease (28). Other adverse effects of lead include: loss of muscle tone, intestinal colic, anemia, spontaneous abortion, possibly cancer (lung cancer, stomach cancer and gliomas), increase in oxidative stress, down regulation of nitric oxide production, interference with vitamin D metabolism and magnesium, calcium, iron and zinc homeostasis, etc.

Lead exposure is most serious for young children because they absorb lead more easily than adults and are more susceptible to its harmful effects. Even low level exposure may harm the intellectual development, behaviour, size and hearing of infants. During pregnancy, especially in the last trimester, lead can cross the placenta and affect the unborn child. Female workers exposed to high levels of lead have more miscarriages and stillbirths.

Sufficient evidence has been accumulated to assume a causal relationship between blood lead level (BLL) and various pathologies. From geochemical data, natural BLL should be at 0.25 μg/dL (29). At this level, lead probably does not cause any harm to humans. At higher concentrations, lead causes a variety of diseases including CVD. Elevated BLL (20-29 μg/dL) correlates with significant increases in all-cause circulatory and cardiovascular mortality (30). Although high blood pressure was previously found to be associated with increased BLL (31, 32), in some studies positive correlation between clinical cardiovascular events and lead exposure was observed at BLL < 5 μg/dL (23). Positive dose-response relationship between low-level exposure manifested by blood levels < 40 μg/dL and blood pressure was observed (33). Delayed responses in central nervous system electrophysiology were related to BLL as low as 15 μg/dL (34). At blood concentration of 33 μg/dL, lead impairs skin wound healing (35). Impaired cognitive functioning and academic achievement were reported among children with BLL below 5 μg/dL (36). Workers could have an average blood lead level of 60.6 ± 8.0 μg/dL, and individuals with average blood lead levels under 63 μg/dL showed signs of peripheral nerve symptoms with reduced nerve conduction velocity and reduced dermal sensitivity.

Notwithstanding the above findings, there is evidence that current BLLs do not reflect total body burden (37). In fact, total lead body burden is mainly represented by bone stores, and bone lead is a better biological marker in chronic lead toxicity. Simple calculations to follow demonstrate that even small BLL, which are quite common for everyday life, are dangerous for human health.

Lead enters human body mainly through gastrointestinal tract and respiratory ingestion. In the USA, at the end of 1980s, an average adult digested about 250-300 μg lead per day in food and beverages (38, 39). About 33% came from food, 16% – from drinking water, 49% – from canned beverages, and 2.5% – from canned food. Notably, in 1970s, the threshold level required for bioaccumulation of lead was estimated to be 100 μg lead per day for infants and 300 μg lead per day for children (40). Digested inorganic lead should overcome hydrophobic barrier to get into the blood. Since specific cellular transporters for lead are unlikely as this metal is nonessential and toxic, lead ions could take the pathways reserved for essential metal ions such as calcium, iron, etc. Indeed, it was shown (41) that intestinal transporter for Fe2+ ions, DMT1, mediates the transmembrane movement of Pb2+.

In Cincinnati in 1960s, the average adult had a respiratory ingestion of 30 to 40 μg per day (39). With 10% of the ingested lead being absorbed from gastrointestinal tract and up to 50% of inhaled inorganic lead being absorbed in the lungs (39), the average combined lead daily body uptake is about 50 μg. Since average adult human body contains about 5 liters of blood and half-life for lead in the blood is about one month (27), the above daily lead uptake results in about 1 μg/dL as a minimal sustained BLL. At first glance, that concentration looks harmless as it is much smaller than the alert levels set by US OSHA (Occupational Safety and Health Association) and other authorities (40 μg/dL for general population and 10 μg/dL for children and pregnant women). Notably, possible uptake of tetraethyl lead and tetramethyl lead, which can easily penetrate the skin (33, 42), was not taken into consideration here.

Once in organism, lead binds mainly to erythrocytes and then moves from the blood to other organs. Lead could be distributed in various tissues and organs including the kidney, liver, spleen, heart, stomach, intestine, bones, and nervous and reproductive systems (22). However, 90-95% of adult body lead burden resides in bones. Human bones mainly consist of calcium orthophosphate (e.g. hydroxyapatite [3Ca10(PO4)6 • Ca(OH)2]), which makes up to 60% of the weight of the human skeleton, comprising 99% of the total calcium of the human body (43). Between blood calcium and bone, the following equilibrium takes place:

$$3\text{Ca}^{2+} + 2\text{PO}_4^{3-} \leftrightarrow \text{Ca}_3(\text{PO}_4)_2$$

Blood lead competes with Ca2+ and forms less soluble lead orthophosphate:

$$3\text{Pb}^{2+} + 2\text{PO}_4^{3-} \leftrightarrow \text{Pb}_3(\text{PO}_4)_2$$
The above equilibria are characterized by solubility products, SP. The deposit cannot be formed, if this product is less than SP. The following equation allows calculating at what concentration in blood lead is not deposited in bones:

$$\frac{[Ca^{2+}]}{[Pb^{2+}]} = \frac{SP_{Ca_3(PO_4)_{2 \cdot (OH)}}}{SP_{Pb_3(PO_4)_{2 \cdot (OH)}}} = \frac{10^{-27}}{10^{-34}} = 5 \times 10^7$$

The values of corresponding SPs could be found in (44, 45). It follows from the calculation that lead is not accumulated in bones at BLL half-million times less than that of calcium. Physiological blood calcium concentration is about 2.4 mM (46). Thus, BLL should not exceed 0.1 μg/dL. Since the above estimated BLL from daily uptake is about 1 μg/dL, lead is permanently accumulated in human bones. Although presented calculation seems quite approximate, it probably has certain merits. Firstly, it closely relates to the natural BLL from geochemical data. Secondly, no threshold value for association between blood pressure and the lowest level of lead exposure has been found yet (23).

It is estimated that about 70% of blood lead comes from skeleton (22). The half-life of lead in bones ranges from a few years in trabecular bone (e.g. the patella) to decades in cortical bone (e.g. the tibia) (47). Therefore, in some instances, bones could provide elevated BLL comparing to lead from daily uptake and serve as an endogenous source of lead exposure in people with increased bone turnover (48). Although both tibia and patella lead were associated with an elevated risk of hypertension, stronger correlation between tibia lead and hypertension was observed (33, 49). Blood lead level could significantly increase when bones become less stable. For example, elderly individuals are experiencing significant bone loss (up to 50% for 70-year-old persons) due to osteoporosis. During pregnancy, it may double due to mobilization from bones. Notably, fetus actively (i.e. against concentration gradient) absorbs calcium and, simultaneously, lead from mother. Bone loss in postmenopausal women and in aged persons could also cause the elevated BLL. In women, lead liberated from the bone as a result of postmenopausal bone loss causes an increase in both systolic and diastolic blood pressures and elevates the risk of hypertension (32).

**MAJOR SOURCES OF LEAD CONTAMINATION**

Lead is ubiquitous in nature and is introduced into living organisms, including the human body, from environment. The total amount of lead that has been dispersed to the world ecosystems through the atmosphere during last 2000 years is $20 \times 10^9$ kg (50, 51). If that amount was uniformly distributed over the Earth surface, which is $510,065,600$ km$^2$, then the average surface concentration of lead would constitute about $40$ kg/km$^2$.

Thus, despite the efforts of developed countries from the early 1970s to reduce lead exposure by the introduction of unleaded gasoline and banning lead-based paint and lead solder in food cans, there is quite a substantial amount of lead accumulated in environment over the years, and this lead could be re-introduced into the atmosphere or dissolved in aquatic systems due to various meteorological and anthropogenic activities.

The major sources of lead exposure include: dietary lead from food and drinks, including drinking water, dust and air emissions. In natural water, typical lead concentration lies between 0.2 and 1 μg/dL (52). However, drinking water can acquire more lead at the original water source, during treatment and/or distribution through the plumbing system. About 16% of lead body uptake come from drinking water (38). A close correlation between the lead concentration in tap water and BLL was found in Hamburg, Germany (53). Data from Glasgow and Liverpool indicated that over 10% of people exposed to an average water lead concentration of 10 μg/dL would have BLL above 25 μg/dL (54). It was known at least 2000 years ago from a Roman architect Vitruvius (ca. 27 BC to AD 14) that «water should not be brought in lead pipes, that is if we desire to have it wholesome». Nevertheless, in 1982 in Great Britain about 45% households used water which had at some stage passed through lead pipes (55). Some properties in Scotland, in 1970s, had lead-lined water tanks in 1970s (55). About 100000-120000 apartments in Hamburg, Germany (53) and 70000 in Paris, France (56) use lead-containing plumbing and are supposed to be supplied with lead contaminated water. In 1993, lead pipes were in use in some 50% of the houses in southern Saxonia, Germany (57). Thereat, the median and maximum lead levels in tap water were 2.4 and 260 μg/dL, respectively. In a study conducted in households in Trondheim, Norway, the highest values of lead were found in hot water from heaters, especially in older houses with old water heaters (38). In 1975-76, 10% of households in England and Wales, and over one-third in Scotland had ‘random daytime’ water lead concentrations above 5 μg/dL (55).

In the USA, drinking water is responsible for approximately 20% of the total daily lead exposure experienced by the majority of population (22). The use of lead solder and leaded pipes from public water supply systems and plumbing was banned in 1986 by the amendments to the federal Safe Drinking Water Act, and lead content in faucets and other brass plumbing components was limited to no more than 8%. Nevertheless, leaded plumbing components continue to be used in schools and daycares creating a significant contribution to lead in drinking water in these buildings. In many Seattle Public Schools, the elevated water lead concentration (>2 μg/dL) was found in 2004 (59). In Philadelphia, 57.4% of public schools had water lead levels exceeding US EPA action level of 2 μg/dL, and 28.7% of schools had water lead levels in excess of 5 μg/dL (60). Interestingly, the EPA jurisdiction does not extend to drinking water in public school buildings (61) and EPA only provides the non-en-
forceable guideline for school that recommends that drinking water lead does not exceed 2 μg/dL.

Traces of lead are found in almost all food (38). Lead can enter food from lead-based glazes on glassware and ceramics, from containers painted with lead-based paint or from vinyl lunchboxes (22). Elevated BLL was found to be associated with storing of food in lead-glazed containers (62), whereas children’s lunchboxes made of soft vinyl were found to contain more than 90 times the legal limit for lead in paint (63). Lead solder used in canned food produced outside the USA and Canada can also contaminate food (64). Lead crystal glassware could also be a significant source of dietary lead, especially when acidic beverages such as wine, port, fruit juices and soft drinks are served.

Dust and soil represent a significant source of lead contamination, especially for young children and workers exposed to lead. Lead in soil comes from the air or from erosion of lead-bearing rocks. Workers in smelters, refineries and other industries and their families living in the vicinity to these industrial enterprises may be exposed to high levels of lead. For example, in children living in highly industrialized city of Duisburg, Germany, BLL was higher (3.1 μg/dL) than in those from the rural area of North Rhine Westphalia, Germany, (2.1 μg/dL) (65). In another case, villagers from Campo de Jales, Portugal, a village surrounding the abandoned Jales mine, had a significantly higher than usual BLL levels that was associated with increased prevalence of respiratory and irritation symptoms (66). Kidney damage in Egyptian policemen was positively correlated with duration of lead exposure from automobile exhaust (67).

Lead-containing dust can be generated from lead-based paints. Most indoor and outdoor paints produced before 1950 contained substantial amounts of lead which sometimes reached 3.8% (68). The lead content of exterior paint is still not regulated. In the USA, lead-based paint covers five billion square feet of non-residential surface area and almost 90% of bridges (22). It is estimated that 38 million homes in the USA contain lead paint. Lead dust can also be generated within the home, especially older homes that used lead-based paints or lead solder.

Atmospheric lead emission and deposition represent the greatest health concern, because of the quantities involved and the widespread dispersion. Airborne lead can be deposited on water bodies, soil and crops, thus entering the animal and, eventually, human food chain. It was shown that 7-40% of the lead in blood is airborne by origin (68).

Although the use of leaded gasoline has decreased dramatically in the developed countries, it is still in use in developing countries and tetraethyl lead remains a common additive to petrol. Leaded gasoline is still legally allowed in aircraft, watercraft, and farm machinery (22). Lead is also released into air through industrial emissions, smelters, refineries and battery plants.

An average residential time of lead in atmosphere is about 4-6 weeks, during which lead can travel long distances and be mostly uniformly distributed over space. The evidences of this has been found in ancient and modern times. For example, lead contents of ice layers deposited in Greenland between 500 B.C. and 300 A.D. were about 4 times that of background, implying widespread pollution of the Northern Hemisphere by emissions from Roman mines and smelters (69). Also, correlation between chronology of anthropogenic lead emission and the lead content in seal hair, penguin droppings and snow was found in Antarctica (50). In individuals living in remote regions of the Himalayas with no known lead exposure, BLL was found to be 0.78-3.2 μg/dL, whereas current median BLL in U.S. adults, ages 20-59, tested in 1999-2002 was 1.5 μg/dL (22). Atmospheric lead deposition strongly depends on weather pattern. For example, two samples of the air collected in Sutton, in vicinity of London, UK, on two different days in the same year contained 29 μg and 7733 μg of Pb per gram of air dust (70). It was raining on both days. This 267-fold difference was due to the fact that wind on the first day was from south-west, and on the second day wind was from north-east and London air was carried over Sutton. Interestingly, Sutton once in a while becomes covered by a thin grey-white deposit originating from the Sahara desert in North Africa. On one particular day, about one million ton of Sahara’s dust was deposited over southern England and Wales (70).

The data on atmospheric lead emission and deposition over European and Trans-Caucasian countries and Kazakhstan could be found on the website http://www.msceast.org/hms/emission.html#Spatial (accessed in January 2008), managed by the Meteorological Synthesizing Center-East (MSC) located in Moscow, Russia. The MSC is an international center of Co-operative Program for Monitoring and Evaluation of Long-Range Transmission of Air Pollutants in Europe (EMEP).

The detailed analysis of the MSC data shows that European countries unequally emit lead (Figure 1). The atmospheric lead emission in most countries in 2004 was less than 0.5 kg/y/km². However, atmospheric lead deposition to a specific country is not proportional to emission, which reflects its strong dependence on weather conditions. As a matter of fact, atmospheric lead deposition is normally distributed over 34 European countries, with most countries getting about 1 kg/y/km² (Figure 2). This suggests pretty good air mixing over Europe. It is of interest to calculate the “lead gain” for each country, i.e. the ratio of atmospheric deposition over the emission. If the gain is more than one, the country gets more lead than it emits, and on the contrary, if the gain is smaller than one, then it country gets less than emits. The results of such calculation are presented in Figure 3. It is evident that most countries acquire more atmospheric lead than is their emission. Notably, Iceland gets 276 times more atmospheric lead than it emits, whereas, at the other end, Portugal gets 3 times less than emits. These data suggest the necessity of tight collaboration and cooperation in fighting against atmospheric pollution.
CONCLUSION

Although there is growing evidence of pathological, in general, and cardiotoxic, in particular, effects of lead, its role as one of the cardiovascular risk factors is not widely recognized. One of the reasons for this is that mechanisms of the harmful activity of lead are not fully understood. Understanding of these mechanisms would place lead among all other widely recognized cardiovascular risk factors and help to develop specialized therapy to prevent its harmful influences. At present, it is not even known whether chemical pollutants influence major risk factors, such as hypertension, cholesterol content or diabetes, or they represent absolute risk for heart disease (7). For this purpose, further investigations are urgently needed.

The necessity to study the mechanisms of biological action of toxic metals comes also from realization that the more we know about lead and the more we understand the mechanisms of its toxicity, the more accurately we can decide what level of BLL is really safe. The advisory BLL established by US OSHA has been gradually decreased over the past few decades, from 60 μg/dL (1960-1970), to 30 μg/dL (1970-1985), to 25 μg/dL (1985-1991), to 10 μg/dL (1991) (71), as the new data on adverse health effects of lead poisoning became available. Recent data indicate that BLL, especially in children, should be reduced even below the 1991 level. For example, it was shown that blood lead and cadmium, at levels well below current safety standards established by OSHA, were associated with an increased prevalence of peripheral arterial disease (72).

In a socio-political sphere, dissemination and popularization of obtained scientific results is also necessary to raise the level of public awareness, since the awareness of ill effects of lead is not widespread. Also, better international environmental regulations and tighter collaboration between countries should be implemented on a global scale to eliminate transboundary atmospheric pollution.
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