Chapter 25

Health Effects of Metals in Particulate Matter

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http://dx.doi.org/10.5772/59749

1. Introduction

There is increased evidence of the association of air pollution and deleterious health effects. Particulate matter (PM) has obtained more attention, especially the small size components (PM_{10}, $PM_{2.5}$, UFP -ultrafine particles-) that carry on their surface different organic and inorganic elements whose composition differ with local and regional variations [1].

PMs might be identified by source, e.g., primary or secondary; combustion products, traffic, or by particle's size (aerodynamic diameter) (PM_{10}, $PM_{2.5}$, UFP -ultrafine particles-). This former parameter is important because the larger the particle the shorter the time it remains suspended in the air and the lower the risk of it being inhaled. Also the smaller the particles the higher the chances of deleterious health effects [1].

1.1. Metals in particulate matter, air pollution and sources

Particles toxic components are complex mixtures of solids or liquids with different characteristics (e.g., mass, number, size, shape, surface area, chemical composition, acidity, solubility). Chemical components may be located on the surface or inside the particle. Considering the source there are natural and anthropogenic emissions. Natural sources include sea salt, volcanic ash, pollens, fungal spores, soil particles, forest fires and wind-blow dust [2]. An-

thropogenic sources consist of fossil fuel combustion products, industrial process, mining activities, wood stove burning and cigarette smoking. In urban areas the main source of PM are motor vehicles especially those derived from diesel fuel combustion.

One of the components adhered to the small particles are metals that come from impurities derived from fuel additives and brakes and tires attrition. Transition metals are generated by non-exhaust emissions, impurities in fuel additives, or metallurgic process. Iron (Fe), nickel (Ni), vanadium (V), chromium (Cr) copper (Cu) are considered because its potential to produce Reactive Oxygen Species (ROS) in biological systems [1]. Others such as zinc (Zn) may also exert toxic effects by other mechanisms besides ROS production.

Heavy metals such as cadmium, lead and mercury are some of more common air pollutants emitted by industrial activities, combustion, extraction and processing activities. The diagnosis of health effects for heavy metals might be difficult if there is no previous evidence of the exposure source, while acute exposures usually occur in the workplace and are more easily identified; signs and symptoms differ within metals because each one interacts with different targets such as: specific metal-binding proteins (metallothioneins, transferrin, ferritin, ceruloplasmin) in cases such as Cd, Cu, Hg, Ag, Mn Zn, Al, and Be; membrane carrier-proteins (phosphate and sulphate-transporters), divalent cation-transporters, some examples are V, Cr, Mo, Se. Heavy metals share with transition metals the possibility to exert its toxic effects by the production of ROS [2-4].

2. Metals and its effects on health

A variety of health effects associated with PM exposure began with the increased mortality risk in those cities with high particulate concentrations (PM), later myocardial infarction incidence and high particulate matter emitted by internal combustion engines were reported. Also ultrafine particles emitted from the vehicles, especially diesel, induced oxidative stress in the endothelium, and through the nose these particles penetrate the olfactory bulb an reached other structures from the nervous system, inducing increased inflammatory responses in the brain. Reduced lung function and respiratory diseases are frequently reported. Thrombosis, hearth rate changes, blood pressure modifications have been associated with exposure to particulate matter also [5] and more recently metabolic abnormalities such as altered glucose metabolism have been reported as well. Low birth-weight, infertility, genotoxicity and cancer [6] are also part of the spectrum of alterations associated with PM. Metals are some of the components adhered to particles surface associated with its toxicity [7, 8]. Here we included the health effects of some metals carried by inhaled particles, and its possible mechanisms of damage.

2.1. Respiratory system and metals

Human beings can survive three weeks without food, three days without water but no more than three minutes without air [9]. As Aaron Cohen mentioned, “You can’t avoid breathing the air no matter what you are” [10] and this comment is because the recent publications about

the air pollution problems reported in China [11] and the case of a Chinese eight-year-old girl diagnosed with lung cancer, until now the youngest victim of lung cancer [10]. Particulate Matter (PM) is the carrier of metals into the lung structure and its content determines its potential health hazard [7].

The exact mechanisms involved in PM exposures and lung damage have been discussed and mentioned previously, but it seems that oxidative stress, inflammation, and modulation of the immune response are some of the mechanisms proposed. Differences according to the age of the population exposed also have some differences because in children's asthma, reduction in lung growth, allergic rhinitis and respiratory infections are more frequently reported compared with adults. Metals such as Cd, Hg and Au have been associated with autoimmune reactions. Other metals reported on the particles are Fe, Zn, and Ni, and recently with the use of the catalytic converters an increase in the presence of Pt, Pd and Rh in the particles inhaled has been observed. These three elements have been associated with asthma, rhinoconjuntivitis, and dermatitis among occupational exposure workers [7].

Lead has been present in the atmosphere in different concentrations and since tetraethyl lead was reduced as anti-knocking agent in gasolines Pb-concentrations in the air and in children ´s blood has decreased [12]. Changes in the ultrastructure of the non-ciliated bronchiolar cell (NCBC) after the inhalation of Pb has been reported along with cell hypertrophy, whorl-like structures and mitochondria cristae disarray [13]. The NCBC was also the target of the combined inhalation of Cd and Pb. A decrease in the cell volume with surface irregularities and the presence of sloughed cells on the epithelial surface were noticed in the exposed group; however at 4-week exposure time, clusters of dividing cells were observed [14]. Differences in the lung concentration of each element, compared with the mixture were reported and could explain the morphological differences reported [15].

Cigarette smoke is a source of direct deposit of metals in lung tissue; because metals are not biodegradable remain in the tissue for long periods of time. In a review from Stavrides [16] chromium, cadmium and nickel are mentioned as carcinogenic and genotoxic metals, indicating that the main effect of these metals as carcinogenic agents is because of altered DNA's repair capacity as a consequence of the oxidative stress. In addition the destruction of the cilia by the gaseous phase of the cigarette smoke facilitates the stagnation of the mucus, whose production increases as a consequence of the irritating effect of the smoke components, resulting in longer periods of cells-metals contact with the increasing opportunity to interact with the genetic material and also to interact with DNA, producing cumulative genetic alterations that could result in lung cancer [16]. Cerium and lanthanum are also reported in the environmental tobacco smoke and may produce inflammation and granulomatosis in lung tissue [17]. Cakmak [18] found association with respiratory effects and the content of Cd, Zn and V in particulate matter ($PM_{2.5}$] and the suggested mechanism was oxidative stress resulting in inflammation and tissue damage.

2.2. Cardiovascular toxic effects of metals

Particulate Suspended matter (PM) exposure raises the risk of developing cardiovascular diseases, both in the short and long term [19, 20]. The proposed mechanisms include inflam-

mation and the induction of hypercoagulability, oxidative stress and endothelial dysfunction [20, 21]. The best evidence that PM have an important role in cardiovascular morbidity and mortality are the interventional studies, in which measures to reduce the levels of PM are taken and a significant decrease in cardiovascular risk is observed [22, 23].

Fine and ultrafine particles are considered the more toxic compared with bigger particles; particularly Diesel exhaust ultrafine particles are dangerous because of its high metals content, causing oxidative stress that leads to endothelial dysfunction and the development of atherosclerosis increasing the risk of heart infarction or stroke [24]. There are associations of elevated concentrations of some metals such as nickel, copper, arsenic, and selenium in fine or ultrafine particles and markers of cardiovascular disease: higher levels of markers of inflammation (C-reactive protein, interleukin-6, and vascular endothelial growth factor) and reduced levels of circulating endothelial progenitor cells (CEPC) suggesting reduced capacity of endothelial repair [25]. Iron overload is directly associated with hypertension, atherosclerosis progression and increased cardiovascular risk [26] Reports that iron chelation with deferoxamine decreases endothelial dysfunction and has been successfully used to reduce cardiovascular risk in diabetic and non-diabetic patients [27]. Lead causes cardiovascular effects even at low doses and it has been associated with hypertension in animals and humans [28]. Peripheral arterial, coronary heart and cerebral vascular diseases had been also associated with Pb exposure, but further studies are needed to establish its causality [29]. Cadmium affects the cardiovascular system too, demonstrated *in vitro* and in animal studies, in addition of epidemiological evidence that Cd is associated with hypertension, promoting atherosclerosis and myocardial infarction. Mercury promotes atherosclerosis and cardiovascular disease in much lower concentrations than those reported for its neurotoxic effects [30].

2.3. Metals and its relationship with cancer

Many epidemiological studies have demonstrated an association between long-term exposure to ambient air pollution and cancer mortality mainly from lung cancer. The risk of cancer is associated with exposure to different pollutants such as nitrogen dioxide (NO_2), Sulphur dioxide (SO_2), particulate matter (PM) and several metals attached to its surface. Metals can promote carcinogenesis, through several pathways such as: producing DNA damage, activating different signaling pathways that lead to tumor progression and promoting inflammation. In the following paragraphs the mechanisms by which some metals promote carcinogenesis are detailed.

Experimental animal studies have demonstrated clearly that cadmium and cadmium compounds by multiple routes of exposure generate cancer at various sites in many animal species and in humans. Cadmium exposures of laboratory animals causes leukemia and lymphoma, local sarcoma and cancer of the adrenal gland, liver, lung, kidney, pancreas, pituitary, prostate and testis. Moreover, cadmium and their compounds are classified by the International Agency for Research on Cancer (IARC) as carcinogens in humans. Cadmium exposure is associated with lung adenocarcinoma, also with prostate, kidney, urinary bladder, pancreas and breast cancer in humans. Several studies have shown that Cd carcinogenicity seems to be crucially mediated by the production of ROS such as hydroxyl radicals, superoxide anions, nitric oxide

http://dx.doi.org/10.5772/59749

and hydrogen peroxide and are due to the inactivation of detoxifying enzymes (e.g., catalase, glutathione peroxidase, glutathione reductase and superoxide dismutase) as a consequence of the interaction with thiol groups. Cadmium is also capable of replacing copper and iron in various cytoplasmic and membrane proteins (e.g., ferritin, apoferritin), leading to an increase in the amount of unbound or poorly chelated copper and iron ions inducing oxidative stress via Fenton reactions. Cadmium also produces genotoxicity by the production of DNA single-strand breaks an damage and competes for binding at sites (specifically with a zinc finger motif) that are important in gene regulation, enzyme activity, or maintenance of genomic stability. In addition, this metal modifies the expression of several genes related to carcinogenesis, including intermediate early-response genes such as c-fos, c-jun, and c-myc; stress-response genes such as metallothionein, and heat-shock genes; genes controlling glutathione and related proteins, as well as transcription and translation factors. Also disrupts cell adhesion mediated by E-cadherin and affects the regulation of cell growth and apoptosis causing tumor progression [31-33]. In addition, cadmium has estrogenic effect and may bind to and activate mammary cell estrogen receptors; it also interacts and regulates the transcription of estrogen-dependent genes affecting the synthesis of proteins and/or the activity of cell-signaling pathways in a manner similar to estradiol [34]. In addition to its endocrine effects on mammary tumor cells, cadmium transforms healthy breast epithelial cells into cells with a cancer-like profile through non-hormone-related pathways. Thus, in the presence of cadmium, the cells alter gene expression and DNA changes in DNA methylation (an epigenetic change) that are typical of cells undergoing transformation from healthy to cancerous type [35].

Furthermore, epidemiological data provide increasing evidence that environmental as well as occupational lead exposures may be associated with increased cancer risk. The IARC has classified lead as possible human carcinogen (group 2B) and its inorganic compounds as probable human carcinogens (group 2A). Lead exposure has been associated to increased lung cancer risk. Some studies looking at blood lead levels in the general population have also found a small increased risk of lung cancer in people with higher lead levels. In addition, the majority of the studies found an increased risk of stomach cancer with higher lead exposure, even though the studies did not take into account other factors that could also have been affected stomach cancer risk. There is a stronger association of kidney tumors with lead exposure; brain, lung and bladder cancer have also been linked to lead in different studies, however results are controversial [36]. Several studies have identified the carcinogenic potential of lead, because the genotoxicity of the metal that induces alterations in DNA synthesis, mutations, chromosome aberrations, as well as inhibiting DNA repair or displacing zinc in DNA binding proteins [37]. Lead, also stimulates cell proliferation, induces alterations in gene transcription and causes oxidative damage that promote carcinogenesis [36].

The International Agency for Research on Cancer (IARC) has determined that some nickel compounds are carcinogenic to humans and that metallic nickel may be carcinogenic to humans. The EPA has determined that nickel refinery dust and nickel subsulfide, are human carcinogens. Occupationally exposed people have a higher risk of respiratory tract cancer (nasal sinus and lung cancer mainly) due to inhalation of nickel at their workplace in nickel refineries, nickel-producing or processing plants or using industries. High cancer risk is related

to less soluble oxidic and especially sulfidic nickel species in refinery dust. Earlier studies gave already indications that rats during two years to inhalation exposure of nickel subsulfide developed a significant higher number of lung tumors [38]. Mechanisms of nickel carcinogenicity have not been fully elucidated yet. Ionic nickel (Ni^{2+}) is supposed to be the carcinogenic species because it can bind to cellular components such as nuclear proteins (histones and protamines) and DNA. Nickel also induces chromatin condensation modifications, DNA hypermethylation, histone acetylation and gene slicing, which disturb gene expression. Moreover, there is evidence that nickel ions inhibit enzymes required for DNA repair. Furthermore, nickel modulates gene expression by the induction of DNA methylation and/or suppression of histone acetylation [38-41].

Some studies have shown that serum copper levels are elevated in cancer patients and correlate with the severity of the disease and the response to therapies [42, 43]. Copper-chelating drugs have been reported to have antiangiogenic activity in animal models. Other study has shown that cancer cells express higher levels of the copper transporter Ctr1 and that the tumors were sensitive to the reduction in systemic copper levels compared with normal tissues [44]. Pharmacological suppression of systemic copper impairs oxidative phosphorylation and tumor growth, since copper can modulate the proliferation of cancer cells and associated tumor growth. It has been proposed that copper can be a rate-limiting nutrient for tumors, similar to oxygen and glucose. Copper levels in tumors affect cytochrome c oxidase activity, additional bioavailable copper facilitates increased production of ATP, which is consumed to fuel rapid proliferation of cancer cells. Thus, copper may not initiate transformation, but may stimulate proliferation of transformed cells by providing energy needed for cell-cycle progression as proposed Ishida and coworkers [42]. Additionally, copper ions are well suited to facilitate formation of ROS that can damage biomolecules, including DNA and chromatin. This event occur *in vitro* with isolated DNA or chromatin, or by exposure of cultured mammalian cells to copper complexed with various agents. Whether if this is likely to occurs *in vivo* is not well defined. However, copper, can directly bind with high affinity to DNA molecule; this binding can modify the conformational structure of DNA promoting carcinogenesis[45].

Mercury and its compounds mainly methylmercury have been classified as "possibly carcinogenic compounds to humans". Mercury has been associated with lung cancer, genitourinary tract cancer and probably brain cancer risk in occupational exposed personnel, however these results are in controversy because workers might be also exposed to other metals [46]. Mercury promotes carcinogenesis inducing oxidative stress. In addition, mercury compounds are genotoxic, mainly by inhibiting the mitotic spindle and altering DNA repair processes decreasing the incision step. Lead and aluminum can increases the toxicity of mercury. It has been shown that mercury rapidly depletes the immune system and could decrease immune tumor response. Chronic exposure to relatively low levels of mercury may inhibit antioxidant enzymatic activity due to persistent oxidative stress. This phenomenon might represent an important peripheral target for mercury toxicity in exposed populations [33].

Inhalation exposures to aluminum in several cohort studies reveal a relationship with increased cancer incidence and mortality in the aluminum smelting industry [47]. The IARC has classified occupational exposures during aluminum production as a causal factor, with

sufficient evidence in humans, for cancers of the lung and the bladder. Nowadays, authors conclude that exposure levels to know health hazards associated with the emissions from primary aluminum production should be studied to establish a clear relationship between inhaled aluminum exposure and cancer [48]. The carcinogenic mechanisms of inhaled aluminum exposure are associated to different compounds an not with the metal *per se*, as it is described in different studies [49].

Chromium is widely used in the industry for the production of stainless steel, chromium plating, and spray-painting. The health effects and toxicity/carcinogenicity of Cr inhalation are primarily related to its oxidation state at the time of exposure [50]. According to epidemiological studies, the hexavalent [Cr(VI) form of this metal, appears to be drastically toxic and carcinogenic, thus it has been classified as carcinogenic to humans by the IARC [51]. The carcinogenicity of the metal is site specific, mainly to the lungs and nasal cavity [50]. The molecular mechanisms of [Cr(VI)-induced carcinogenesis are well studied and characterized, and the main mechanism of chromium carcinogenesis, is the production of free radicals, resulting in the generation of oxidative stress, This stress causes a series of modifications that are directly linked to the establishment of the cancer phenotype. The genetic changes involve Cr-DNA adducts, formation of DNA-protein cross-links, single and double strand DNA breaks [52, 53].

Studies exploring excessive environmental exposure to iron are often limited by poor characterization of the environmental factors and causal relations to effects other than the chemical properties of the iron [54]. Iron is present primarily in two oxidation states, ferrous ions [Fe(II) and ferric ions [Fe(III). Mechanisms by which iron may contribute to tumor induction or progression, includes oxidative damage-induced changes in genetic material as the initial step involved in Fe-induced mutagenesis and carcinogenesis. Other mechanisms are alterations in gene expression consistent with increased iron requirements in proliferating cells and decreased immune surveillance against cancer [55].

In occupationally exposed individuals, inhalation of Mn is a potential important route of exposure [56]. In general, Mn and its inorganic compounds are considered to possess low mutagenic or carcinogenic potential compared with other heavy metals. The experimental evidence on its carcinogenicity does not provide any clear evidence, while the available occupational and environmental epidemiological evidence is equivocal as to whether exposure to inorganic Mn is associated with a significant cancer risk or not [50]. Apparently from *in vitro* data, Mn and some inorganic Mn compounds are cytocytotoxic at differing concentrations depending on the test system, generating ROS *in vitro* and *in vivo*, interfering with DNA polymerases, mitochondrial function and activating some cytokines and MAPK cell signaling cascades. These mechanisms should probably contributes to Mn carcinogenesis, but further studies must be made [57].

Finally, V is a major transition element that is released primarily by the burning of fossil fuels, including petroleum, oil, coal, tar, bitumen, and asphaltite. Among V compounds, V pentoxide is highly toxic [58]. The IARC classified vanadium pentoxide as a possible carcinogen to humans (Group 2B) in 2003 [59]. The pentavalent forms, such as V and vanadate have carcinogenic potential via ROS generation, DNA damage, and activation of hypoxia signaling

[51, 60]. There is *in vivo* preclinical data on cancer chemoprevention and therapy, which provide a rationale for its use in human populations [61].

2.4. Genotoxicity and metals

The term genotoxicity refers to any detrimental change in genetic material, regardless of the mechanism by which the change was caused [62]. The DNA lesions can be classified according to the extent and severity of damage. Repairable damage includes single-stranded breaks, oxidized bases, AP-sites and alkali-labile sites. The damages that result from the incorrect repair are chromosomal rearrangements and sister chromatid exchange. Finally, there are irreparable injuries including gains or losses of whole chromosomes or chromosome fragments (chromosomal aberrations) that are the product of clastogenic or aneugenic events. The consequences of DNA damage include alterations in the three-dimensional conformation, blocking the processes of replication and transcription, deletions, chromosomal instability, cell death and mutagenic events. Thus, genotoxic mutagenic events precede and therefore are the source of cellular malignancy [63]. Studies indicate that nickel induces chromosome aberrations in rats [64]; cadmium [65] and lead [66] causes single strand breaks and alkali-labile sites in mouse cells; in rats uranium causes double strand breaks [67]; iron induces in mice chromosome aberrations and micronuclei; in human beings vanadium produces bases oxidation and micronucleus [68], but in mice produces single strand breaks and micronucleus too [69, 70]. Conversely to others metals, titanium showed no adverse effects on DNA in mice cells [71].

2.5. Neurotoxicity of metals

The brain is vulnerable to oxidative stress damage produced by metals, due to its great metabolic activity, high cellular content of lipids, and low levels antioxidants such as catalase and superoxide dismutase. Air pollution is a mixture of gases and metals associated with particulate matter (PM) [72] that induced olfactory dysfunction, neuroinflammation and elevated markers of neurodegeneration [73] and heavy metals in PM are accumulated in brain tissues [74].

Inhaled nanosized particle (NSP) includes ambient spherical particles < 100 nm deposited directly on olfactory dendritic cilia in the olfactory mucosa. Subsequently uptake and translocated along axons of the olfactory nerve by nasal route via neuronal transsynaptic transport and uptake through the blood brain barrier from systemic circulation, and induced oxidative stress and gene expression in central nervous system in human and experimental animals [75, 76].

Occupational and environmental exposure to neurotoxicants such as iron (Fe), copper (Cu), manganese (Mn), aluminum (Al), zinc (Zn) mercury (Hg), lead (Pb) and vanadium induced oxidative stress [77, 78] that generated accumulation of ROS inducing protein, lipid and deoxyribonucleic acid (DNA) oxidation, and produced neurotoxic changes that are risk factors for development neurodegenerative diseases such a Parkinson (PD), Alzheimer (AD), Huntington (HD), amyotrophic lateral sclerosis (ALS) and transmissible spongiform encephalopathy (TSE), [79, 80] [81, 82].

Protein misfolding is implicated in neurodegenerative diseases, such as amyloid-β precursor protein, in senile plaques and tau in neurofibrillary tangles of AD,α-synuclein in Lewy bodies in sustantia nigra in PK, prion protein in TSE and huntingtin in HD striatum have been connected to neuronal iron homeostatic control [83].

At a molecular level metal dishomeostasis and mitochondria dysfunction in AD and PD and the cytoplasmic predominance of neuronal 8-hydroxy-Guanine supports mitochondria as the major source of ROS responsible for RNA oxidation and might induce DNA oxidation neuronal damage [84, 85].

Atmospheric Mn is present in gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) is a putative modulator of dopamine biology (the primary target of Mn neurotoxicity) and workers exposed to airborne Mn are in risk of developing PD known as manganism, an extrapyramidal neurological disease characterized by rigidity action tremor, bradykinesia, memory and cognitive dysfunction. Mn in blood crosses the blood brain barrier and accumulates inside the neuron disrupting the synaptic transmission and inducing glial activation[86].

In previous studies it has been reported that aluminum inhalation induced altered of expressions of glycogen synthase kinase-3 (GSK3) and protein phosphatase (PP1), which help in the regulation of carbohydrate metabolism in the rat's brain [87]. Mercury exposures in male marmoset monkey showed deposits of Hg in ventral horn motor neuron and atrophy of large myelinated motor axon [88]. In our mice model the inhalation of vanadium pentoxide caused morphological and functional alterations in the central nervous system. In the olfactory bulb we showed dendritic spiny loss of granule cells and ultrastructural changes characterized by swelled organelles, disrupted mitochondria and necrotic and apoptotic neuronal death that might correlate with the olfactory dysfunction. Also, the hippocampal formation showed a decrease in dendritic spines and necrosis of the pyramidal layer of CA1 and granule cell of dentate gyrus that could be related with spatial memory impairment at a 4-week exposure. We also found the loss of immunoreactive- tyrosine hydroxylase + in substantia nigra and a decrease in dendritic spine density in the medium striatal spiny neurons at 8-week exposure time. The blood brain barrier (BBB), after the inhalation of vanadium showed cilia loss, cell sloughing and ependymal epithelium detachment from the basal membrane, and the presence of oxidative damage in the choroid plexus, which was confirmed by the presence of 4-hydroxynonenal. The reported alterations were associated with an increase in MMP-9 and MMP-2 activity in the cortex, the olfactory bulb, hippocampus and striatum [89, 90].

2.6. Metals and mental health

Environmental pollution by heavy metals that are produced by the combustion of hydrocarbons is a public health problem, which affects different organs such as central nervous system [91] have resulted in behavior, learning, mental disorders, attention deficit and low mental performance [92-94].

Inhaled metals involved in centrals nervous damage, mental and behavioral disorders are arsenic, lead, cadmium, mercury, manganese and vanadium [95] [96]. The inhalation of these

metals induces brain damage and resulted in behavioral disorders associated with the severity of the poisoning, the metal involved, the chemical state of the element as well as the exposure route and the age of the exposure [97]. Inhaled arsenic might cause Guillain-Barre similar syndrome with confusion, irritability, cognitive loss, decrease in verbal responses and paralysis [98].

Lead causes an irreversible reduction in cognitive ability in children resulting in an IQ decrease [99]. Oxidative stress is also the mechanism proposed to induce the damage [100]. Other behavioral effects induced by inhaled-Pb are depression, irritability, bipolar states, mental retardation and cognitive deficit [101].

Cadmium has the ability to replace iron and copper, which induces an increase in the production of ROS via the Fenton reaction, which translates into GABA and serotonin systems alteration, causing irritability, depression, amnesia and cognitive disorders [102].

Mercury mechanism of action are not fully known but it seems that interact molecularly with the antioxidant systems such as GSH, cysteine and melatonin [103]. Apoptosis, necrosis, lysis and phagocytosis have been reported in exposed humans [104]. Other neurotoxic effects reported are weakness, inability to concentrate, lethargy, depression, irritability, blindness, coma and death [105].

Excessive manganese exposure during childhood causes hyperactivity and learning disorders [106]. Studies in animals show that inhaled manganese reaches the central nervous system through the olfactory nerve and by the blood, crossing the blood-brain barrier inducing [107] "manganism" that includes tremor, “manganic madness", schizophrenic symptoms, violent behavior, compulsions, emotional instability, hallucinations, and other psychiatric disorders [108].

Vanadium brain accumulation has been related with behavioral and cognitive disorders, [109] [110]. Memory loss, a decrease in the sense of taste and Parkinson’s disease has been reported in vanadium exposure [111, 112].

2.7. Metals and its toxic effects in the eye

Despite the fact that the eye is an important air pollutant target because it is directly exposed to the atmosphere, as well as to the elements that enter into the lungs and further are distributed through the systemic circulation [113], until now, only two studies have been found to approach the effect of atmospheric pollutants inhalation on the retina, where phototransduction process takes place. Such studies were performed in a mice model in which the animals were exposed to vanadium (V) [0.02M] inhalation 1 h twice a week, for 4, 8 and 12-week time periods.

In all exposure times, morphological alterations in the photoreceptor layer (PL) and in the inner and outer nuclear layers were observed, as well as a gradual rhodopsin pigment reduction in the PL and an increase of the oxidative stress biomarker -4-hydroxinonenal- in the PL and in the inner and outer plexiform layers [114].

Additionally, the effect of V exposure was evaluated on the Müller glial cell (MGC), which is the predominant radial glia in the retina, for 4 and 8-week time period. Glial fibrillary acidic protein (GFAP) expression increased at four weeks after the exposure, probably as evidence of reactive gliosis, whereas it was observed a gradual reduction in Glutamine synthetase (GS) expression as exposure time passed. Given that GS is an enzyme whose levels are regulated by its substrates -glutamate (Glu) and ammonium- its reduction might suggest that photoreceptors, that produce most of the Glu in the retina, are degenerating in response to the V toxic insult [113]. This is consistent with the rhodopsin pigment reduction that previously was mentioned, because it evidenced damage to the photoreceptors as a consequence of the increase in the oxidative stress induced by the exposure [114].

2.8. Metals and glucose metabolism

There is limited information about the role of metals in carbohydrate metabolism and glycemic regulation; however there are some studies showing that metals have hypoglycemic or hyperglycemic effects. The relevance of studying these effects is that the exposure to some metals has been related to increased risk of diabetes, but some other metals have shown a hypoglycemic effect and have been studied as a potential treatment of diabetes (as vanadium).

Iron, mercury, nickel and lead are hyperglycemic metals that are also pollutants and will be discussed in this chapter. Iron is an atmospheric pollutant in both urban and industrial sites [115], near iron or steelmaking industries, near petrochemical areas [116], cement mills and in metro systems of many cities [117]. Mercury is a toxic heavy metal widespread and persistent in the environment and it is considered one of the most relevant atmospheric pollutants (Wang et al, 2006). Nickel is a metal released from many industries and it has proved to be toxic at high concentrations and lead is a heavy metal pollutant because it is released to the atmosphere by the burning fossil fuels, industries and mining activities.

Iron is an essential metal for life, but iron overload is a health risk because it is associated to insulin resistance, hyperglycemia and an elevated risk of type 2 Diabetes Mellitus [26, 118, 119]. Several authors have explored the mechanism of this risk; oxidative stress has been implicated because it is associated with insulin resistance and with direct damage on beta pancreatic cells [120].

There is evidence that mercury can cause hyperglycemia because it can directly damage pancreatic beta cells inducing necrosis or apoptosis [121]. In a follow-up study of young people who were exposed to high levels of mercury a higher risk of developing diabetes after 18 years was found [122]. The majority of the associations are related to water pollution, but it is important to evaluate people who have been exposed by atmospheric pollution. On the other hand, there is no evidence of higher levels of mercury in blood of diabetic type 1 or 2. A causal relationship between mercury and pancreatic dysfunction that leads to hyperglycemia and diabetes has been reported, but not all the diabetics have higher levels of this metal [123, 124].

There are reports about the effect of lead on glycaemia regulation but the effect seems to be related to the dose and the compound. Ibrahim and cols in 2012 [125] had reported hyperglycemic effect on rats exposed to different doses of lead acetate, just as Adham et al. did in birds

in 2011 [126], however other authors have found in rats hypoglycemia, after low doses of lead dissolved in water [127]. It is necessary to understand the mechanism and the reason for this dual effect.

There are multiple reports of hyperglycemia and insulin resistance after exposure to nickel in different animal models [128, 129], so it is important to consider this element as a possible risk factor to glycemic deregulation.

Some metals decrease the levels of blood glucose such as vanadium, chromium, magnesium and zinc. Proposed mechanisms for this effect include: activation of insulin receptors, increasing insulin sensitivity, and function as cofactors or components of the enzymatic systems involved in glucose metabolism or acting as antioxidants to prevent tissue peroxidation. [130].

Vanadium potentiates the action of insulin and lowers blood glucose levels. Some vanadium compounds have been studied as antidiabetic agents [131]. At first it was thought that vanadium exerted an effect on the glycemia because it inhibits appetite at certain concentrations, but hypoglycemia was observed only minutes after its administration, which is not a period of time sufficient to exert its anorectic effects [132]. The hypoglycemic effect is explained because vanadium inhibits some tyrosine protein phosphatases increasing the phosphorylation levels of various insulin pathway intermediaries. Activation of these signaling pathways results in GLUT transporter translocation to the plasma membrane [133]. Another factor that contributes to the hypoglycemic effect of vanadium is its inhibitory effect on gluconeogenesis because it inhibits the expression of the gluconeogenic enzymes PEPCK and GTPase [134]. There are reports of severe hypoglycemia that may threaten life in vanadium acute intoxication [135]. Further studies are needed to evaluate the hypoglycemic effect of vanadium as an air pollutant or in workers occupationally exposed.

Chromium induces hypoglycemia because it is a promoter of glucose catabolism in muscle cells and adipocytes. Also, it functions as a regulator of glycaemia in different animal and human models, and as an inhibitor of glucogenolysis in muscle cells. The trivalent compounds as chromium picolinate increase insulin activity [136]. There are reports that after the consumption of Chromium based compounds; patients suffering from diabetes improved their sensibility to insulin [137]. The mechanisms studied are: 1) increase the concentrations of the messenger RNA for insulin receptor; 2) making a complex with insulin that has a greater activity in the metabolism of glucose than insulin alone; 3) through the decrease in TNFα, resistin and interleukin 6 concentrations; and 4) increasing the sensitivity of pancreatic β-cells [138, 139]. There are no reports of severe hypoglycemia, but further studies are needed to elucidate the effects of chromium in concentrations inhaled as atmospheric pollutants.

Depletion of magnesium is associated to insulin resistance, hyperglycemia and type 2 Diabetes [140]. Low levels of serum magnesium in diabetics is associated with poor glycemic control [141] and foot ulcers [142]. Zinc has insulinomimetic activity *in vitro* and blood glucose lowering effect *in vivo* [143]. In some studies zinc deficiency has been associated with hyperglycemia and diabetes [141]. Also, zinc supplementation in diabetic patients improves glycemic control [144]. However, a higher zinc concentration has promoted metabolic syndrome (overweight, hypertension and dyslipidemia) in Wistar rats [145] Ugwuja et al, in

2014 [141] reported higher zinc levels in complicated diabetic patients compared with diabetic uncomplicated cases. The meaning of these associations is unclear and needs further studies.

2.9. Metals and its toxic effects on liver

Inhaled air pollutants that travel through the blood, also produce changes in the integrity of liver parenchyma, which leads to a slowly and irreversible liver damage [146] [147]. Acute or chronic liver damage is the usual consequence in the majority of the toxic agents that enter into the organism, because the liver is the main organ that metabolizes xenobiotic agents such as metals. The progressive deleterious events in the liver starts with steatosis ending in hepatocellular carcinoma, passing through chronic hepatitis, fibrosis and cirrhosis, finalizing in liver failure and death [148].

It is important to emphasize that regardless the etiological agent in all types of liver damage there is overwhelming evidence of an increase in free radicals or a decrease in antioxidant defenses [149]. As well, the reactive oxygen and nitrogen species play a crucial role in the induction and progression of the liver diseases.

Arsenic is a metalloid that has been characterized by causing a variety of alterations in the organism [150]. Arsenic crosses lung alveolar membrane and reaches the blood stream; hence it is transported to all the organs, mainly to the liver, in which is metabolized. It has been reported that arsenic induces liver cancer [151]. This is done through the modulation of transcription factors like NF-kB, AP-1 and p53 that promotes liver tumors. Likewise, Arsenic causes liver lipoperoxidation producing large amounts of ROS [152]. Also a decrease in the levels of the superoxide dismutase enzymes (SOD), catalase (CAT) and glutathione peroxidase has been reported [153].

Lead has been characterized by inducing damage by the production of ROS, that increases lipid peroxidation and decreases antioxidant defenses [154]. It has been reported that lead damages the cell membrane of hepatocytes and its DNA [155].

Cadmium causes liver damage mainly by induction ROS inducing lipoperoxidation via Fenton reaction [156]. The increment of ROS induces DNA damage, proteins oxidation and lipoperoxidation. Cadmium replaces iron and copper in the Fenton reaction. It is also capable of moving to zinc from proteins and changing their structure [157]. Chronic liver exposure to cadmium induces liver failure [158].

Mercury toxicity is the consequense of its high affinity to sulphydric groups in proteins and enzymes involved in cell cycle progression [159] [160]. It induces hepatocyte apoptosis causing acute liver failure [161].

Liver is the main organ for the metabolism of iron and it is also the target of its pathological accumulation, as a consequence of a metabolic disease, such as hemochromatosis or because of an increased exposure [162]. Iron accumulates in the hepatocytes in which induces the formation of hydroxyl radicals (.OH) from reduced forms of O_2, ending in oxidative stress [163].

Cooper is associated with Wilson's disease resulting in its liver accumulation, because of the reduced metal elimination by bile duct [164]; air pollution exposure also causes liver accumulation and injury [165]. Copper and iron share the same mechanism of damage causing an increase in reactive species in liver parenchyma ending in fibrosis and cirrhosis [166].

Vanadium is other metal that alters liver function, inducing ROS via Fenton reaction, damaging proteins and altering the genetic material [167]. Inhalation of V_2O_5 induces alterations in liver function tests with an increase in ALT y AST, as well as hepatic megalocytosis [168].

2.10. Pancreas and metals

Pancreatic parenchyma damage by metals has been poorly analyzed, but some reports mention acute and chronic pancreatitis, and cancer [169]. The pathophysiology and etiology of pancreatic damage are still unknown, and usually are lethal [170] [171] [172]. Vanadium induces an increase in pancreatic enzymes, hypertrophic acinar cells, which results in an acute pancreatitis [173].

2.11. Immunotoxicity of metals

Urban populations are often exposed to metals as constituent of particulate matter (PM), one aspect of the myriad toxicities that might arise from these exposures is altered lymphoid system and thus immune responses. Among the metals that when inhaled damage the lymphoid system we can find vanadium, cadmium, mercury, iron, lead, manganese, chromium, copper and arsenic.

Among the main effects of vanadium that our group has reported we can find splenomegaly. Spleens of mice exposed to vanadium showed morphological changes that included an increase in the size of the white pulp, germinal center hyperplasia, and an increase in the size and number of megakaryocytes and CD19+ lymphocytes. In the same study we found a decrease in the mice capacity to star a humoral immune response, when presented to Hepatitis B surface antigen (HBsAg), vanadium exposed mice presented higher antibodies concentrations with lower affinity compared to controls [174]. On the other hand, our group, in the thymus, has reported morphological changes. We found that vanadium exposed mice presented a shift of the normal cortex-medulla relationship, showing a much thinner medulla and the presence of medulla-like areas within the cortex regions. These changes suggest an alteration of the immune response [69, 89]. In addition to these findings we have reported a decrease in the presence of CD11c, a dendritic cell marker, and MHCII an antigen presenting cell marker, in the thymus of vanadium-exposed mice. This study was conducted using two methods, immunohistochemistry and FACS, with similar findings. This hyperplasia downturn could be detrimental for the negative selection of thymocytes, as dendritic cells are closely related to this process, leading to the persistence of self-reactive cells and increased risk of autoimmune diseases [175].

On the other hand, it has been shown that mice exposed to low concentrations of cadmium have an enhanced humoral immune response [176], however, exposing rats to high concentrations of Cd results in the decrease of B and T cell function and impairment of the phagocytic

http://dx.doi.org/10.5772/59749

capacity of NK cells [177]. Chronic exposure to Cd increases serum concentrations of diverse pro-inflammatory cytokines such as IL-1β, TNF-α y la IL-6. Chronic exposure has also been associated to splenomegaly, alterations in the histology of the spleen and the appearance of giant cells and fibrosis. In the thymus, atrophy evidenced as a decreased weight of the thymus has been reported with this metal. All these toxic effect can lead to disturbances in the immune selection and response [178].

One of the worst threats mercury inhalation imposes, is the development of autoimmunity in genetically predisposed individuals, chronic exposure is capable of inducing an immunosuppressive state, alongside apoptotic defects that can lead to a syndrome similar to that of Lupus. The mechanism through which this occurs is not entirely understood. It has been proposed that Hg can associate with proteins creating large complexes capable of activating the immune system, this is specially true for molecules present in antigen presenting cells leading to a massive activation of T cells [179]. Hg is not only capable of inducing immunosuppression, it can also induce immunostimulation in both, mice and humans, its exact mechanism is not known yet [180].

Iron is an essential element for metabolic processes occurring in both, human and microbial cells. Therefore it's relationship with immune function is evident. There is an hypothesis that the persistence of certain extracellular pathogens in circulation induces an iron restriction in the mononuclear phagocyte system, blocking its phagocytic capacity. As a result changing concentrations of Fe in the system cause by exposure to this metal could alter the immune function [181].

Lead exposure through inhalation can affect the immune system, an increase in circulating concentrations of IL-4 and IFN-γ and leukocytosis have been reported in a murine model [182]. The effects of lead on the immune system have been studied using macrophages. Being present in a diverse range of tissues, any adverse effect on them could be associated with several presentations. It has been shown that lead diminishes the phagocytic capacity of macrophages, which plays a central role in innate immunity, and therefore could redirect the response towards a Th2 or antibody producing response which could in turn favor the development antibody mediated autoimmunity. In the presence of lead NO decreases and with it the macrophages capacity to kill pathogens. Due to Pb the membrane of erythrocytes gets damaged leading to anemia by increasing the rate at with the spleen phagocytes damaged red cells. It has been reported that macrophages can increase their production of TNF-α due to Pb exposure, and with these can damage peripheral tissue. This has been proven in two models; in the first peritoneal macrophages exposed to Pb damaged liver tissue and in the nervous system Pb exposed microglia damaged peripheral neurons [183].

An immunosuppressive state has been documented in workers exposed to Mn inhalation. In an experimental model using rats, Mn decreased circulated populations of CD4+ and CD8+ lymphocytes that could explain the immunosuppressive state reported in the work exposure studies [184].

Other metal with immunotoxic properties is Chromium. Occupational exposure to this metal can lead to an imbalance of the humoral and cellular components of the immune response. In

a study conducted on workers exposed to inhaled Cr, it was found that circulating levels of immunoglobulins and complement components were different when compared to their controls. Seric titers of IgG and IgA were lower than those found in the control group, whilst C3 and C4 concentrations were higher. These results suggest that exposure to Cr can produce ill effects on lymphocytes that include inhibition of immunoglobulin secretion and complement activation [185].

Copper inhalation by humans is more frequently found as an occupational exposure. This metal can cause morphological changes in lymphoid tissue. In a murine study Cr inhalation led to an increase in spleen weight and decrease in thymus weight. Morphologically splenomegaly and thymus atrophy were also reported. All of the above could lead to an immunological imbalance [186].

Studies with Arsenic have been conducted using pregnant women that live in rural areas contaminated with this metal. In this study their IgG titers were elevated compared to non-exposed pregnant women from a different region. The study suggest that a higher titer of IgG can increase the pregnant women mortality, however, the overall effect on humoral response that these elevation in IgG can have is still unknown [187].

The immune system is an important and complex system composed of different kind of cells and factors whose function is of the outmost importance in preserving health. This system is on of the most sensible targets of atmospheric pollution. Metals associated with particulate matter can cause an ample specter of immunological disorders. The susceptibility to these disorders, however, can be deeply related to a genetic predisposition in the individual.

2.12. Reprotoxicity of metals

Air pollution has been related to adverse effects on female reproductive health such as infertility, miscarriages, delay menarche [188] and an increased risk of hypertensive disorders during pregnancy [189]. Metals contained in particulate matter could be related with these reproductive alterations [190], because it has been proved that some metals like cadmium, lead, mercury, manganese, chromium and nickel have female reprotoxic effects [191].

Cadmium increased the duration of estrous cycle in rats exposed to 1 mg Cd/m^3 (NTP, 1995); as well as after 6 weeks of exposure to 1 mg Cd/m^3 and after 18 weeks after exposure to 0.16 mg Cd/m^3 (5h/5 days/20 weeks) [192]. Female mice exposed to 230 μg Cd/m^3 daily showed a lower incidence of pregnancies, and a lower level of serum 17-β estradiol [193]. Inhalation of 1 mg Cd/m^3 (5 h daily/5 days weekly/5 months) caused a decreased female rats fertility [194].

Mercury vapor has reproductive effects in occupationally exposed women (dental assistants and dentists), reports included abortion, stillbirth and menstrual disorders (irregularity, painful or hemorrhagic menstrual bleeding) [195]. Polymenorrhoea or oligomenorrhoea [196] and reduced fertility [197] it was also observed in women working in a lamp factory and dental assistants, respectively. In animal models, Davis and coworkers [198] observed longer estrous cycles in rats exposed to 2 mg Hg/m^3 (2h/day/11days).

Female workers at a lead smelter showed an increased frequency of abortions and their child showed low birth weight [199]. In pregnant women living in Mexico City, high levels of lead in maternal blood were related with an increased incidence of abortions [200]. Vigeh and coworkers [201] observed high levels of lead and manganese in pregnant women diagnosed with preeclampsia.

MnO_2 dust inhalation augments the number of pups and decreased their body weight gain, when female rats were exposed preconception [202]. In other study rats transfer manganese to their offspring trough milk, after preconception exposure to manganese inhalation [203].

Inhaled chromium caused menstrual alterations, postnatal hemorrhage and delivery complication in female workers and near-resident women [204]. In female workers at a nickel refinery plant, it was observed an increased incidence of abortions [205]. In other study, high levels of nickel were found in women with endometriosis [206].

Vanadium inhalation caused an increased length of estrous cycle in females exposed to 4.5 mg V/m^3, and exposure to 9 mg V/m^3 reduced the number of females with a normal cycle (NTP, 2002). After inhalation of V_2O_5 0.02M (1h/week/4 weeks) female mice get into anestrous and showed lower serum levels of estradiol and progesterone and an increase in the width of uterine stroma and myometrium [207]; as well as an increase in the lipidic peroxidation in the ovary and a reduced size of secondary and preovulatory follicles [208].

Bucher and coworkers [209] studied the effect of inhalation of copper sulfate (3 mg/m^3, 6 h daily, 5 days per week for 13 weeks) in rats; they find alterations in sperm (decreased motility and abnormal sperm increase) and in testicular weight.

In male rats exposed to inhalation of $MnSO_4$ (3 mg/m^3) for 6 h/day for 7 days a week, Dorman and coworkers (2001) quantified an increase in the concentration of $MnSO_4$ in the testes of treated animals (0.79 ± 0.18 μg / mg of dry tissue) compared with the testes of control animals (0.32 ± 0.04 μg / mg of dry tissue).

In mice exposed by inhalation of lead and cadmium has been reported mitochondrial damage in Sertoli cells of mice exposed to inhalation of lead acetate (0.01 M, 1 h / week/4 weeks) and chloride cadmium (0.006 M, 1h / week / 4 weeks); in addition, mitochondrial alterations were more severe and an detected earlier in animals exposed together to both compounds than in controls [210].

In mice exposed to inhaled vanadium pentoxide (0.02 M) for 1 h twice a week, for 12 weeks, alterations were observed in the cells of the seminiferous tubules: necrosis, pseudo-nuclear inclusions and disruption of cellular junctions [211]; alterations were also found in proteins of the, such as decrease of gamma-tubulin [212] and actin [213].

In humans, it has been proposed that exposure to toxic metals is a risk factor in reproductive health. A study by Akinloye and coworkers [214] indicated that the cadmium concentration in serum and seminal fluid from azoospermic men was higher than in oligozoospermic and control men.

In the case of lead, there is evidence of its reproductive toxicity effects in humans. Occupational exposure to lead causes decreased sperm motility and dysfunction of the sex glands [215].

2.13. Teratogenesis

During the last decade, epidemiologic studies have researched the connection between air pollution and its adverse effects during pregnancy, being found an increase in preterm birth risk, low birth weight and foetus underdevelopment; however, results are contradictory because of different methodological approaches [216]. A study held in California showed the link between the expose to PM2.5 and low birth weight in children born at the end of pregnancy. The particles had sulphide, sulphate, vanadium, iron, manganese, bromine, ammonium and zinc. These particles can affect the fetus weight because of their impact in cardiovascular and respiratory health in the mother, produce oxidative stress and damage the fetus DNA, affecting in its development [217]. An experimental study of mouse in utero exposure to diesel emissions, a pollutant that cause the major number of PM2.5 suspended particles, demonstrated that there is embryonic reabsorption and placental changes such as hemorrhage, necrosis, swelling and oxidative stress. In adulthood it was found propensity to arterial hypertension and cardiac failure in mice that were exposed to diesel during prenatal development [218].

Waste incinerators produce environmental pollutants such as heavy metals, specifically cadmium, lead, mercury, chromium and arsenic. A study held in Cumbria, UK, found and excessive number of perinatal and child mortality because of spina bifida and cardiac malformations near to incineration places [219].

Heavy metals can produce health problems because of oxidative stress (Cd, Cr, Pb, As), neurological damage (Pb, Hg), DNA damage (As, Cr, Cd), changes in the metabolism of glucose (As) and calcium (Cd, Pb) and interfere with essential elements (Cd, Hg) [220]. It is because of this that these metals have a teratogenic potential, which depends also on its placental transportation. The placenta is an active transporter of essential elements, such as calcium, copper, zinc and iron, as well as toxic elements such as cadmium, lead, mercury and nickel. Heavy metals can go through the placental barrier and accumulate in the fetus tissues and amniotic fluid.

Cadmium accumulates in the placenta, and it has been found a correlation between cadmium levels and the expression of the metallothionein, which retains the cadmium and prevents that it reaches the fetus; but its increase blocks the transportation of Zn to the fetus, decreasing the placental permeability to this essential element. Cadmium also affects the synthesis of the placental hormones such as progesterone and leptin, affects the trophoblastic cells migration and induces an early development on the decidua of the endometrial stroma [220]. The maternal exposure to cadmium during pregnancy is linked to preterm birth, intrauterine growth restriction and low birth weight [220, 221]. In experimental models it has demonstrated that it can affect the embryo development and the implantation. Cadmium increases in rats the oxidative stress and decreases the antioxidant enzymes activity [221]. The exposure of rats to cadmium during the organogenesis period produces external and internal malformations, as well as alterations in the ossification. After birth it was observed an alteration in males and females sexual behavior [222, 223]. The exposure to cadmium in human fetal gonads in culture produces a decrease of germinal cells due to apoptosis, but it does not affect the cells proliferation [223].

Lead can easily go through the placental barrier by simple diffusion. Lead can affect calcium-mediated processes in the syncytiotrophoblast; it accumulates there and reduces the cytochrome oxidase activity, an enzyme of the respiratory chain, reducing therefore the ATP production in this cells. Lead produces oxidative damage and induces preterm birth, abortion, intrauterine growth restriction and congenital abnormalities [220]. Chromium that can be found in the polluted air has been linked to neuroblastoma in children [224].

Arsenic has been linked to miscarriage, low birth weight and malformations in populations working or living near foundries in which emissions arsenic can be found. In animal models arsenic produces toxicity in development, since it produces malformations, intrauterine death and intrauterine growth restriction. These malformations include neural tube defects, gonadal and renal agenesis, eye defects and malformations of the ribs [225].

Manganese can be found in the air due to, essentially, diesel combustion. Manganese goes through the placental barrier by simple diffusion. Manganese is an essential nutrient, and that is why it can be found in the tissues and fluids of both, mother and foetus. The lack or excess of manganese affect the prenatal development. Because of the air pollution an excess of manganese has been linked to intrauterine growth restriction during the foetal period and, postnatally, to hyperactive behavior, decrease of intellectual ability and alteration of the psychomotor development [226]. Experimental studies have showed that the excess of manganese has a teratogenic effect, since that produces growth restriction, embryonic death and bone alterations [227].

High levels of iron during the human embryonic period can be teratogenic. Iron is toxic mainly because it produces oxidative stress. Iron catalyzes the production of hydroxyl-free radicals, which destroy cells by lipid peroxidation, enzymes denaturation, carbohydrates depolymerization and ruptures in DNA. Experimental studies in the mouse show that an increase of iron produces histological alterations in the encephalon, as well as spine and ribs malformations [228].

Equally, high levels of nickel affect the mouse embryo development, producing embryonic death, fetal death, and malformations such as hydrocephalus, eyelids alterations, microphthalmia, exophthalmia, clubfoot, umbilical hernia and bone anomalies. The excess in nickel ions can replace other metals required for the structure and functions of enzymes, which get inactivated, and this could be the cause of the embryo and fetus toxicity observed in mice, rats and women [229].

Vanadium causes reproductive damage. It goes through the placenta, constituting complexes with transferrin or albumin, and accumulates in the placenta and the fetal tissues. It has been found that vanadium affects the prenatal development, since it produces embryo mortality, fetus toxicity and teratogenicity in mice, rats, hamsters and chickens [69, 89]. In humans, it has been proved that the exposure to vanadium during pregnancy is linked to low birth weight. In the chicken embryo, the vanadium pentoxide produces embryo mortality and teratogenicity, since it provokes alterations in tubulation and the central nervous system, microphthalmia, abnormalities in the pharyngeal arches and facial development processes or their derivatives, congenital heart defect, limbs malformations and visceral ectopia [89]. Vanadium produces

oxidative damage in proteins, lipids and DNA, interferes with DNA repair and affects cellular signaling pathways and cells proliferation [230].

3. Conclusion

Metals enter into the respiratory system adhered to particulate matter, and by this route they reach the systemic circulation. In the blood metals are attached to proteins or ionized entering into the different organs and cells producing a variety of outcomes. The chemical characteristics of the inhaled metals, the length of the exposure, the route, and the physiology of each organ will determinate the metabolism, the affected functions and the possible manifestations, which are resumed in Figure 1. Some metals interact with enzymes inhibiting its actions by the interaction of the metal with the SH group of the enzyme or by displacement of an essential metal cofactor; another interference mechanism is the inhibition of the synthesis of the enzyme, indirectly altering the systemic function; the binding of the metal by certain cytosolic proteins may modify its toxicity. Also metals may interact directly with the components of the cell, and may be accumulated in the lysosomes, or damaging the mitochondria and inhibiting respiratory enzymes leading to cell death. A direct interaction with DNA may produce gene mutations, chromosome aberrations or aneuploidy; these changes could pave the way to proliferation and cancer development [231].

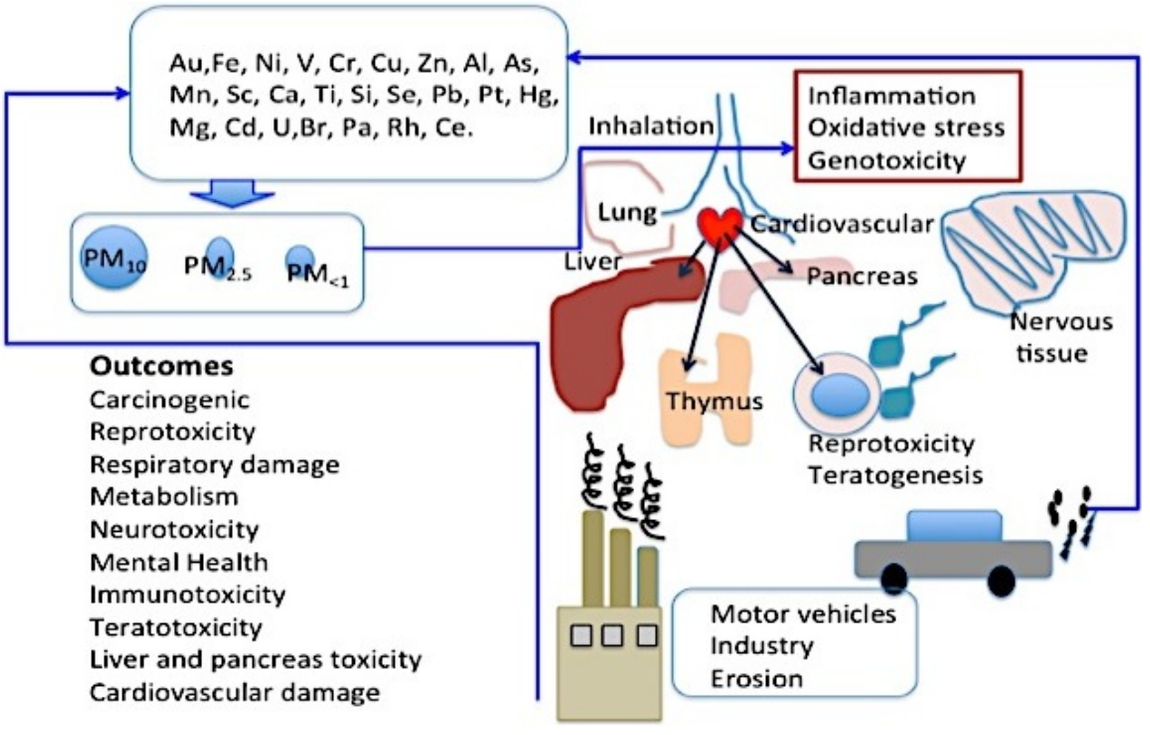

Figure 1. Interaction of metals in particular matter that enters into the respiratory system inducing inflammation, oxidative stress and genotoxicity. The sources and possible outcomes are resumed.

The problem of metals associated with atmospheric particulate matter is not new and there are increasing reports about its health effects, as we have mentioned in the previous sections. Even though the toxic effects of these elements are severe, there are scant specific knowledge about the association of a disease and the inhalation exposure. This problem needs more research in order to count with more information for understanding the mechanisms of damage and to propose measures to control the emissions, decrease the exposure and its adverse effects.

Acknowledgements

Authors thank Alejandra Núñez-Fortoul for reviewing the final English version.

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