Chapter 7

Occupational Exposure to Coal, Genotoxicity, and Cancer Risk

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Abstract

Coal is a heterogeneous mixture containing large quantities of organic and inorganic matter, including carbon, hydrogen, oxygen, sulfur, nitrogen, and organometallic forms. The presence of mineral matter in coal may result in a number of environmental and human health problems related to its mining, preparation, and combustion. During coal mining activities, large quantities of coal dust, ashes, polycyclic aromatic hydrocarbons (PAHs), and heavy metals are released into the environment, forming a complex mixture. This mixture becomes one of the most important occupational risks for the health and safety of workers due to its synergistic, additive, and enhancing effects. Once inside the organism, this cocktail-like mixture can interact with cellular mechanisms related to the production of reactive oxygen species (ROS) and can cause damage in important macromolecules such as DNA, lipids, and proteins. In this review, human populations exposed to coal and coal burning were analyzed. Data from different studies were evaluated in relation to the effect of complex mixture exposure on DNA damage and mechanisms, and the background factors, such as gender, age, or smoking habit. The high temperatures that occur in combustion processes affect the characteristics of the resulting particles. The coal fly ash is released by combustion and its composition varies depending on the coal type and the method of collection used such as electrostatic precipitators. Compounds such as PAHs once activated by the organisms have been shown to have mutagenic and carcinogenic activity due to its ability to form adducts with purines. Moreover, metals that commonly are evaporated during the cooling process increase its toxicity. The particles when inhaled can pass from the alveoli into the bloodstream and affect extrapulmonary organs. Several studies have described the inflammatory cascade that triggers exposure to coal and coal fly ash particles; they have a complex composition capable of generating a persistent inflammatory process, resulting in diseases widely described as emphysema, bronchitis, pneumoconiosis, asthma, and cancer. Several human biomonitoring studies have been conducted evaluating the inflammatory process and

the release of cytokines, polymorphisms involved in detoxification mechanisms, different biomarkers associated with occupational exposure, DNA damage, and the influence of oxidative stress in disease development. The relationship between chronic exposure to coal and coal ash particles and cancer is still widely debated. This review gave us a broad assessment about the associated mechanisms between cancer and exposure to coal and different findings around the world.

Keywords: coal, biomonitoring, DNA damage, ROS, PAHs, diseases

1. Introduction

In the last decades, the human population genetics integrity has been compromised by the great industrial activity, which exposes people to a variety of chemicals and genotoxic agents. As a result, it is important to determine what is considered as an "acceptable" level of genetic damage in a concrete population, carry out assay genotoxicity as a routine and also monitor those who, by their occupation or lifestyle, are more exposed or with a bigger risk of having alterations on their genetics stability [1].

One method to quantify the exposure to those substances, as well as its possible impact on the organism, is the use of biological monitoring procedures, or biomonitoring, through biomarkers. Biomonitoring studies try to establish a connection between the environmental factors and the diseases. They detect first alterations in nonmalignant phases, so as to prevent health problems by recognizing the environmental cause of them.

The biological markers, or biomarkers, are the measurable changes (biochemical, physiological, or morphological) that associate to a toxic exposure or any early biochemical alteration, whose study on the biological fluids, tissues, or exhaled air that allow to assess the health risk exposure intensity. The identification of genotoxicity markers believed to cause genome damage is useful, since it can define a prepathogenesis state, such as cancer. It is of vital importance for different diseases prevention, which is the final goal of biomonitoring. In order to achieve it, there must be two stages: 1) detecting human exposure to environment carcinogenic agents; 2) determining genotoxic effects *in vivo* [2].

The combined use of genetic biomarkers and classic epidemiology tools (clinic history and questionnaires) has enabled the identification of early effects to the occupational exposure to distinct pollutant around the world [2–4]. Many biomarkers are used to assess genotoxic effects on human populations exposed to complex mixtures of chemicals. Although there are different possibilities, micronuclei (MN) frequency, chromosomal aberrations (CAs), and comet assay are the most commonly chosen biomarkers. MN originates from chromosome fragments or whole chromosomes that are not included in the main daughter nuclei during nuclear division [5, 6]. MN induction reflects clastogenic and aneugenic damage and is a predictive biomarker of cancer risk [7]. Comet assay detects DNA lesions in individual cells obtained under a variety of experimental conditions; the technique can also be used to evaluate DNA repair [8, 9].

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The large inter-individual variability in the capacity to activate or inactivate potential genotoxic and carcinogenic compounds is probably influenced by polymorphisms of the genes encoding the metabolizing enzymes. Genes and proteins involved in metabolization/detoxification of xenobiotics, as well as those involved in DNA repair, are usually used as potential markers of susceptibility for the development of several diseases in which the etiology is related to exposure to environmental hazards. Polymorphisms in such genes have been linked with an increased risk of cancer in several case-control studies [10].

Biomonitoring studies in populations exposed to complex mixtures of chemicals considering individual susceptibility are quite complicated due to inadequate toxicity data, and the unpredictable nature of interaction effects that may be synergistic, additive, or enhancers.

2. Occupational exposure to coal

The coal reserves in a worldwide level is up to 847.5 billion of tons, enough amount to serve the current production for 119 years. This prediction is different from the ones related to oil and gas, which have available supplies for less time [11]. According to data from the International Energy Agency (IEA), coal is the most used resource for energy generation in the world, responsible for 41% of the total production. Nowadays, the main application of mineral coal is to generate energy through thermal power plants. These reserves are considered to have a 109-year lifespan and their coalfields are located in 75 countries. The main world coal producers are China, the United States, India, Australia, Indonesia, Russia, South Africa, Germany, Poland, and Kazakhstan, which are responsible for 91% of the world's production [12]. If those projections are right, the consequences of coal mining and combustion will have large effects in the environment. Thus, the exposed populations monitoring is fundamental with the aim of contributing to the state of knowledge about the health risk and motivate the establishment of control, hygiene, and prevention strategies.

It is well known that coal mining activities are one of the biggest resources of contamination due to the large quantity of substances liberated in the environment. The content of the coal dust and ashes produced by burning are not always homogeneous and this depends on the source and rank of the coal [13, 14]. Coal dust is constituted from carbon, hydrogen, oxygen, nitrogen, quartz (crystalline silica), and inorganic minerals, such as beryllium, cadmium, cobalt, chromium, iron, boron, copper, nickel, antimony, zinc, aluminum, titanium, magnesium, manganese, mercury, and lead [15]. As observed, coal is a mixture of a variety of chemicals, including hydrocarbons, which may raise polycyclic aromatic hydrocarbons (PAHs). All technological processes associated with open fire or temperatures between 400 and 600°C, that may lead to PAHs, should be considered potentially hazardous [16, 17].

In relation to coal mining residues exposure, studies in which biomarkers of effect, susceptibility, and exposure are used as epidemiological tools remain rare and a big part of them come from studies on underground coal mining [18, 19]. The effects generated by open coal mining are little explored, though. In open coal mining, the residues pass directly to the atmosphere, where complex mixtures are formed, and the coal exposure to environmental factors such as

sunlight facilitates the processes of spontaneous combustion and, therefore, the release of PAHs [20].

Studies about the coal exposure and its harmful effects have been conducted around the world [21–23]. The main way for exposure of the coal mining workers to the potentially dangerous residues is through the inhaling of coal dust particles from mining and manipulation. It is a known fact that the coal mining continuous exposure can cause a variety of diseases, such as coal workers pneumoconiosis (CWP), silicosis, cancer, and chronic obstructive pulmonary disease (COPD), as emphysema and chronic bronchitis [24].

Many studies have established that some of those diseases could have been originated from the genotoxic damage generated by the inhalation of those mineral particles, able to interact with macrophages, epithelial cells, and other cells generating the production of large amount of reactive oxygen species (ROS) [24–26]. The continuous inhalation of coal dust and fly ashes particles is an important cell and non-cell source of ROS in the lung. This may be associated to the damage of target cells of that tissue and other cell lines, after spreading through the bloodstream [27].

Coal-induced DNA damage is related to macrophage activation and the recruitment of polymorphonuclear cells. This cell activation induces the release of inflammatory mediators, such as cytokines, ROS and reactive nitrogen species (RNS). The proinflammatory properties of ROS and RNS include endothelial cell damage, lipid peroxidation and oxidation, the release of chemostatic factors, the recruitment of neutrophils, and DNA damage [26, 28]. Interaction of ROS with DNA can result in DNA structural and transcriptional errors [29, 30]. Damage caused by ROS is recognized by DNA glycosylases, apurinic/apyrimidinic endonucleases of the base excision repair (BER) mechanism, and in some cases, by the nucleotide excision repair (NER) machinery, leading to DNA strand-breaks [31, 32].

Although chronic exposure may continue to damage the DNA, it has been suggested that inorganic elements can induce DNA single-strand breaks, possibly via the generation of ROS and that this type of damage is soon repaired. Metals are also known to modulate gene expression of enzymes [33]. In addition, PAHs can induce DNA lesions as single-strand breaks via DNA repair mechanisms, related with increased adduct formation and electrophilic metabolites [34–36]. Electrophilic metabolites covalently interact with the DNA [37, 38], and adducts are formed with purines, especially guanine, after metabolic activation by enzymatic complex P450 [39]. The International Agency for Research on Cancer (IARC) classified quartz, main constituent of coal, into IARC Group 1 (carcinogen), due to sufficient evidence for carcinogenicity in experimental animals and in humans [40, 41]. The other factor that could lead to different results in coal dust exposure, with positive and negative results, might be explained by the possible differences in composition, in which the proportion of the metals, PAHs, and silica (quartz) content may have an influence on the genotoxicity. Despite those findings, coal dust remains classified as non-carcinogen for human (Group 3) in IARC [40, 41]. The importance of coal as an energy source makes its characterization and estimation of risks of extreme importance to the safety of those individuals and the environment.

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Several factors may explain conflicting results among different studies with human exposed to coal, e.g. cigarettes smoked, age, gender, nutritional status, and individual polymorphisms [6, 42]. Susceptibility is critical to an understanding of coal diseases, including cancer, and many xenobiotic agents act to alter susceptibility. Unknown individual susceptibility, inadequate toxicity data, and the unpredictable nature of interaction effects make the implementation of a human biomonitoring assessment for complex mixtures of chemicals extremely complicated.

3. Oxidative stress and genotoxic damage related with coal exposure

One important aspect to consider about the coal exposure is the amount of products generated during the coal combustion. The burning of coal, in order to generate electricity, produces flue gasses and particulate materials like coal fly ashes and residues as scoria and bottom ash. The finer particles (coal fly ash) are obtained by mechanical or electrostatic precipitation of the dust in suspension in the gases produced by combustion, while the coarser particles fall to the bottom by gravity and are removed at the bottom of the boiler [43, 44].

The combustion temperature is an important factor that determines the physical properties of the particles. In the combustion of conventional high temperature (>1400°C), the main aluminosilicate melts and condenses to form spherical particles. The coal fly ash particles produced are mostly irregularly shaped and contain a complex mixture consisting of unburned carbon; oxides; quartz; elements such as aluminum, silicon, calcium, iron, nickel, arsenic, chromium, copper, lead, cadmium, zinc [45, 46], and PAHs [47].

The coal fly ash has a relatively low toxicity as compared with coal or quartz [45]. Studies have determined the role of coal fly ash particle size and the release of iron, which leads to generation of radicals and oxidative stress. In this context, it was demonstrated the ability of coal fly ash release of bioavailable iron, which triggers processes and redox oxidant production [48]. In addition, it was shown that interleukin 8 (IL-8) levels in human lung epithelial cells are increased in response to coal fly ash and vary with the bioavailability of iron, as a function of source of coal and particle size [49]. The smaller size fraction had more stimulatory activity, which may be related to the fact that iron is more concentrated in this fraction. Particle size is a critical factor because a larger surface area allows more significant transport of metal and other adsorbed components, increasing the pulmonary toxicity of particulate matter (PM) [50].

The particles are classified according to their aerodynamic diameter (in micrometer) in coarse (PM 10), fine (PM 2.5), ultrafine (PM 0.1) [51]. The smaller particles are more harmful with respect to health effects because of their very high alveolar deposition fraction, large surface area, chemical composition, ability to induce inflammation, and potential to translocate to the circulation to extrapulmonary organs [52–54]. These particles could trigger persistent lung inflammation compared to the coarse particles in addition to the exposure to genotoxic compounds, which are contained in the particles [26, 55].

Depending on the toxicity, the chemical properties, and the concentration in air, coal and coal fly ash particles can constitute a risk to exposed workers. When these particles are inhaled and

deposited in the lungs, they can lead to health risks due to the leaching of genotoxic compounds and altered immunological mechanisms affecting the lung parenchyma causing diseases [56]. These nanometric particles are very small, which allows them to penetrate the biological organs and affect its normal function. More specifically, as the particle load in the lung increases the alveolar macrophages and epithelial cells are activated, leading to the release of inflammatory mediators, ROS, enzymes (elastases, proteases, collagenases), cytokines [tumor necrosis factor alpha (TNF-α), interleukins], and growth factors (TGF-β) that control and stimulates the fibrosis, genotoxic events, and cell death [45, 57, 58].

Persistent inflammatory processes have been accepted as a crucial factor in the pathogenesis. In Zhai et al. [59], was investigated whether systemic TNF-α, soluble TNF-α receptors (p55, p75), IL-6, and soluble IL-6 receptor could be markers of biological activities of Chinese CWP. Interestingly, those results suggest that serum levels of TNF receptors and IL-6 are associated with the fibrotic process of CWP and serum cytokine levels may be correlated with the severity of CWP. In the pathogenesis of these respiratory diseases related with coal exposure, oxidative damage plays a key role. Either acting in association or independently, the chemical and physical characteristics can lead to the generation of ROS and oxidative stress [60, 61].

These particles are chemically heterogeneous and can be a source of oxidants by themselves ("acellular" mechanisms), due to their composition, such as oxides, metals, and PAHs [26]. Soluble metals (transition) associated to the particle can increase the generation of ROS by Haber-Weiss reactions. PAHs may be metabolically activated and induce ROS and oxidative stress, also forming bulky adducts or strand breaks on DNA [50, 62, 63].

Another way of generating oxidants is via cellular. Once in the lungs, alveolar macrophages are activated and generate large amounts of ROS, and chemoattractant factors of other inflammatory cells such as monocytes and neutrophils are released, which amplify this response generating more oxidants [64]. The particle size is a critical factor, because very large particles are difficult to phagocytose, leading to the process of incomplete or "frustrated" phagocytosis aggravating the response [65, 66].

Considering three different scenarios with respect to exposure to particles, the generation of oxidative stress, inflammation, and oxidative DNA damage, several authors questioned whether the lung inflammation may be related to secondary genotoxic effects. They also questioned if phenomena of oxidative stress, inflammation and DNA damage are independent or interrelated, whether oxidative stress stimulates inflammatory processes, or inflammation mediated by particles cause oxidative stress, or even if it is possible that particles may cause both phenomena of oxidative stress and inflammation but for different mechanisms of action [26, 61].

In normal physiological conditions, there is a balance between ROS generation and antioxidant defenses. However, the continuous inhalation of particles may interfere in this equilibrium leading to oxidative stress process in the lung. Consequently, a high loading of particles alters the oxidant-antioxidant balance, leading to oxidative damage and the beginning of pathological processes [67]. The most important effects of ROS in the lung include damage to cell

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membranes by lipid peroxidation process, protein oxidation, and DNA damage in target cells [27].

As seen in **Figure 1**, oxidative DNA damage can have many consequences, from cell death and tissue destruction to cell proliferation. Furthermore, ROS can also act as regulators in signaling pathways intracellularly and transcription factors of a variety of genes including those of proinflammatory cytokines, adhesion molecules, and proto-oncogenes [68].

In vitro effects induced by coal exposure have been described in different cells such as murine alveolar type II epithelial cells (C10) [69] and in 7TD1 cells [70]. ROS generation and oxidative damage by coal fly ash particles have been described in different cell lines, in human peripheral blood mononuclear cells [71], in rat alveolar macrophages (NR8383) [72], in BEAS-2B human lung epithelial cells [73], and in rat lung epithelial (RLE) cells [74].

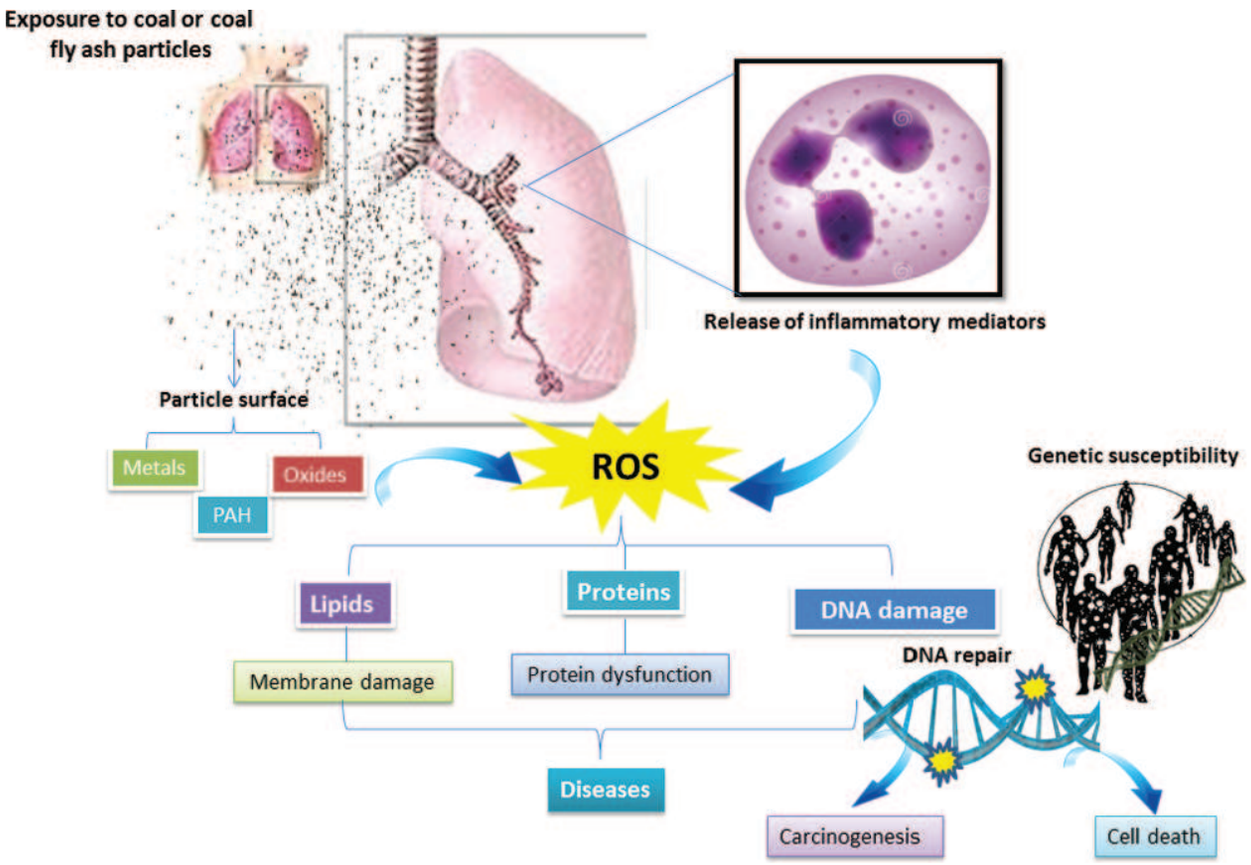

Figure 1. Main pathways associated with the generation of oxidative damage and the development of diseases induced by coal and coal fly ash particles.

ROS induce point mutations and CAs in cells. Many inhaled toxic substances contained in the particles contribute to oxidative modification that has as target of attack specific components of the cytoplasm and the nucleus. Such changes include DNA breakage, DNA oxidative modification, base modifications, alterations in the DNA sequence, poly-ADP ribosylation, activation of kinases, activation of proto-oncogenes, and inactivation of tumor suppressor

genes. Persistent generation of ROS generated by mineral particles indestructible or engulfed incompletely leads to damage to organelles keys [59, 61, 75]. The oxidation of C8 deoxyguanosine (dG), resulting in 7-dihydro-8-oxo-2′-deoxyguanosine (8-oxodG), is the most common oxidative lesion generated by ROS. The proportion of 8-oxodG/dG has been considered as a biomarker of oxidative stress and has been studied in relation to exposure to mineral particles *in vitro* and *in vivo* [76].

Human biomonitoring studies about the effects of exposure to coal and residues using different biomarkers have been conducted around the world. In this context, our group has obtained interesting findings in workers exposed to coal mining in Colombia and Brazil. In Rohr et al. [77], was found that Brazilian workers with occupational exposure to coal had significantly increased genetic damage in peripheral blood lymphocytes compared with unexposed individuals. Exposed workers presented lower average levels of thiobarbituric acid reactive substances (TBARS) and catalase activity (CAT). In addition, DNA damage evaluated by human buccal micronucleus cytome (BMCyt) assay was observed in mine workers, which could be a consequence of oxidative damage resulting from exposure to coal residue mixtures [78].

In Colombia, DNA damage in lymphocytes of coal open-cast mining workers using the cytokinesis-blocked micronucleus test and the comet assay were observed [79]. Also, in buccal mucosa samples, the micronucleus frequencies and nuclear buds were significantly higher in the exposed group than in non-exposed control group. Interestingly, blood samples of Colombian mining workers analyzed showed higher values of silicon and aluminum characteristic elements of coal particles, compared with the control group [80]. All these studies converge to a point: the compounds contained in the particles may be related to ROS generation, DNA damage, and formation of pro-mutagenic adducts.

These are important findings if we consider that oxidative DNA damage can lead to long-term risk of cancer and other diseases caused by air pollution by these particles. In **Table 1**, can be observed an overview of key studies on the genotoxicity in human population exposed to coal and coal combustion products. These studies demonstrated DNA damage using different methods, related with inorganic elements and oxidative stress.

References	Country	Exposure(s)	Biomarker	Outcome(s)
[81]	Slovenia	_	Sister-chromatid exchanges (SCE), unstable chromosome and chromatid aberrations and micronuclei in blood lymphocytes	Significantly higher levels of chromosomal aberrations, SCE and micronuclei in exposed group compared with the control group.
[82]	Brazil	Underground workers directly exposed, surface	Oxidative stress biomarkers (TBARS, GSH/GSSG, α-tocopherol, GST, GR, GPx, SOD, CAT).	The results showed that subjects directly and indirectly exposed to coal dust face an oxidative stress condition. They also indicate that people living in the

References	Country	Exposure(s)	Biomarker	Outcome(s)
		workers indirectly exposed, residents living near the mines.		vicinity of the mine plant are in health risk regarding coal mining-related diseases.
[22]	Turkey	Coal combustion products	Chromosomal aberrations (CAs), polyploidy, sister-chromatid exchanges (SCEs), and micronuclei (MN) in blood cells.	Significantly higher levels of CA, polyploidy, SCE, and MN in peripheral blood lymphocytes of workers compared with controls.
[83]	Turkey	Underground coal mining	SCE, CA, and micronuclei frequencies in peripheral lymphocytes.	Increase in sister chromatid exchanges, chromosomal aberrations, and micronucleus frequencies found in underground coal miners as compared to control group.
[21]	China	Indoor smoky coal emissions that contain high levels of polycyclic aromatic hydrocarbons (PAHs)	GSTM1 and GSTT1 genotypes. Expression of p53 protein in sputum samples.	The GSTM1 null genotype may enhance susceptibility to lung cancer due to these indoor coal combustion emissions. Smoky coal use was strongly associated with overexpression of p53 in tumor cells among highly exposed women.
[79]	Colombia	Open cast mining	(MN) frequency and DNA damage (comet assay) in lymphocytes.	The biomarkers evaluated showed statistically significant higher values in the exposed group compared to the non-exposed control group.
[80]	Colombia	Open cast mining	Micronucleus (MN) frequencies, nuclear buds, karyorrhectic and karyolytic cells in buccal mucosa samples and content of inorganic elements in blood samples by PIXE.	MN frequencies and nuclear buds in buccal mucosa samples were significantly higher in the exposed group than in the non-exposed control group. In addition, karyorrhectic and karyolytic cells were also significantly higher in the exposed group (cell death). Blood samples showed higher values of silicon (Si) and aluminum (Al) in the exposed group.
[84]	Russian	Underground coal	Chromosomal and chromatid type	A higher frequency of chromosomal aberrations in the exposed group

References	Country	Exposure(s)	Biomarker	Outcome(s)
		mining	aberrations in blood lymphocytes	compared with the control group.
[77]	Brazil	Open coal mining	MN and nucleoplasmic bridge frequencies in peripheral lymphocytes, damage index and damage frequency (comet assay).	Increased MN and nucleoplasmic bridge frequencies in peripheral lymphocytes, increased damage index and damage frequency (comet assay). Lower average levels of TBARS and catalase activity (CAT), while the mean superoxide dismutase activity (SOD) levels were higher in the exposed group.
[78]	Brazil	Open coal mining	Buccal micronucleus cytome (BMCyt) DNA damage, cell death, and basal cell frequency in buccal cells.	The exposed group presented a significantly higher frequency of basal cells, micronuclei in basal and differentiated cells, and binucleated cells compared to the non-exposed group. No correlation between DNA damage and metal concentration in the blood of mine workers.
[19]	Peru	Underground coal mining	Chromosomal aberrations in peripheral lymphocytes	Miners occupationally exposed to underground mining activity have an increased frequency of chromosomal aberrations compared with the controls.
[85]	_	Coal fly ash particles	SCE frequencies in peripheral blood lymphocytes.	No increased SCE frequencies were found in PBLs of workers potentially exposed to coal fly ash when compared to the control group. No differences were observed between the exposed and control groups for frequencies of gene mutations at the HPRT locus in PBLs, for micronucleus frequencies using the cytokinesis block method, or for urinary mutagen excretion measured with *Salmonella typhimurium* tester strains TA98 and TA97.
[86]	Germany	Underground coal mining	Structural chromosomal aberrations in peripheral lymphocytes	Coal miners had significantly higher frequencies of chromosomal aberrations compared with controls.
[87]	Turkey	Underground coal	Sister chromatid exchange (SCE) and	SCE and MN frequencies in CWP patients were found significantly higher than

References	Country	Exposure(s)	Biomarker	Outcome(s)
		mining	micronucleus (MN) frequency in lymphocytes of Turkish CWP patients.	in coal workers and unexposed groups.

Table 1. Overview of key studies on the genotoxicity in human population exposed to coal and coal combustion products.

4. Conclusions

The coal mining activities generate different types of compounds that are released into the environment. Once into the atmosphere, these compounds form a complex mixture that consists of metals, oxides, and PAHs. These compounds can interact with "acellular" and cellular mechanisms related with ROS production. The metals found in the coal fly ash and coal particles by different ways lead to the ROS formation. Important macromolecules as DNA, proteins, and lipids can suffer oxidative modifications. The PAHs contained in the particles also influence the particles toxicity. A second indirect way for excessive ROS formation is related to cellular mechanisms, which is consequence of oxidative burst of macrophages and neutrophils during phagocytosis of particles and inflammation produced.

If we think in exposed populations, we cannot ignore the social and environmental impact associated with coal mining. The continuous inhalation, the high load of particles in phagocytic cells, the oxidant-antioxidant imbalance which are linked to the origin of pathological processes; this whole scenario is worrisome to biologic level for these populations. In addition, in recent years, coal mining had a remarkable increase in demand; international mining companies have increased their investments in exploration around the world. For this reason, human biomonitoring studies in exposed populations become really necessary to contribute to knowledge state about the risk for those people in order to motivate the design of control, hygiene, and prevention strategies, besides epidemiological surveillance.

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