Academy of Romanian Scientists *Volume 10, No. 1, 2021, pp. 60 - 89*
Annals Series on Biological Sciences ISSN 2285 – 4177

REVIEW

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Atmospheric Pollution and the Impact on the Respiratory Tract and Lungs

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DOI https://doi.org/10.56082/annalsarscibio.2021.1.60

Abstract

The rapid development of the infrastructure of metropolises, cities, population and industry has led to severe air pollution, which has serious consequences for public health and the environment. Distortion of environmental quality includes a wide range of particulate matter (PM) and nanoparticles (NPs) that may contain in their structure and on their surface toxic substances, nasopharyngeal secretions, heavy metals, manure, pollen, bacteria, viruses, cigarette ash, SOx, NOx, O3. Studies in the literature on epidemiology and toxicology show the association between air pollution and its negative impact on the respiratory tract and lungs. This review highlights the pathways of PM and NPs (nasal, buccal and skin pores) and also the mechanisms by which their negative effects are strictly related to the complex properties and very small size of particles. Exposure to PM and NPs in both the short and long term can lead to clinical, chronic and even incurable diseases causing even death. This review addresses a topical issue that may influence both the understanding of the negative impact of air pollution and the improvement of protection strategies for dealing with an ecological disaster.

Keywords*:* Atmospheric pollution, PM, nanoparticles, respiratory tract, pulmonary diseases

Introduction

Environmental pollution is one of the most serious problems in which the quality of life and proper functioning of living ecosystems is deteriorated under the action of natural factors and socio-industrial activities caused by the population. People's actions regarding air pollution have led to changes in balance and natural quality with repercussions on health. The urban way of life of the developing cities has led in recent years to emissions of PM10 material particles (particles with aerodynamic diameter ≤ 10 μm); PM2.5 (particles with aerodynamic diameter ≤ 2.5 μm), PM1 (particles with aerodynamic diameter ≤ 1 μm) and nanoparticles NP <0.1μm (e.g. gold nanoparticles, silver and carbon nanoparticles, micelles, liposomes, nanoemulsions), aerosols, gases (CO, SO_x, NO_x, O_3) and other toxic substances [1-5]. The problem of air pollution must be treated with great seriousness and responsibility with regard to the mentioned pollutants because they are able to penetrate the respiratory tract and to break through all the protective barriers to the blood flow and to be directed to the other organs. The danger is great because their surface is a platform for binding toxic substances, manure, purulent suppurations, heavy metals, hydrocarbons [6, 7]. The degree of danger is also given by the dimensions, the physico-chemical properties, the sources of origin, the chemical composition and the mode of exposure [8]. Poisoning of the human body and organisms is visible and can be proven by scientific studies.

The pollutants of interest in this research are PM2.5 and nanoparticles which are currently the most discussed and studied in terms of ambient air quality. The progress of research has highlighted the effects on human health causing lung, cardiovascular, cancer and other diseases. The toxicity of fine fractions is highlighted by their ability to penetrate living tissues, which shows that their presence in atmospheric air can be extremely dangerous [9]. The impact on the environment also has its mark on climate change, the reduction of visibility and solar radiation, the influence and contribution to the deterioration of monuments and vegetation, acid rain [10]. The nature of these pollutants is very diverse and depends on the emitting sources. The presence in the atmospheric air is largely due to natural sources (dust, fires, volcanic eruptions, rock disintegration) and anthropogenic (construction sites, road traffic, agricultural activities) [11-13]. The level of impurity should not exceed the maximum limit allowed by the legislation in force for PM2.5 (20 $\mu g/m^3$) but for nanoparticles there are currently no legislative norms.

The World Health Organization (WHO) has estimated that 8 million people worldwide have died from the effects of air pollution and epidemiological studies have shown the interactions of PM2.5 and NPs in the air with the body during

exposure [14]. The the loss of such a large number of lives is a big problem. We must consider improving air quality by educating the public, which would lead to awareness of the seriousness of the problem, reducing polluting activities, phytoremediation which is the simplest and most natural way to combat pollution, frequent washing of urban streets, improvement of infrastructure, etc. These measures can ensure an improvement in the health of the population and living organisms. It all depends on human nature and the desire to do well.

Route of entry of PM and NPs into the human body

PM and NPs can enter the human body through inhalation, ingestion and skin pores [15, 16]. These pathways are highlighted in Figure 1, through a simple and comprehensive scheme, Figure 1a, and an explanatory model of effective transport in the body, Figure 1b. Both PM and NPs are able to penetrate the body's protective barriers to reach the bloodstream and through it to other organs whose functioning can affect it over time. The ability of NPs to penetrate these barriers is due to their physicochemical properties, size, morphology, surface chemistry and agglomeration. Although the Environmental Protection Agency divides PM into two major categories, PM10 with a maximum annual allowable limit of 40 $\mu g/m^3$ and PM2.5 with a limit of 20 $\mu g/m^3$, it should be noted that there are several classes of PMs that are not yet regulated [17].

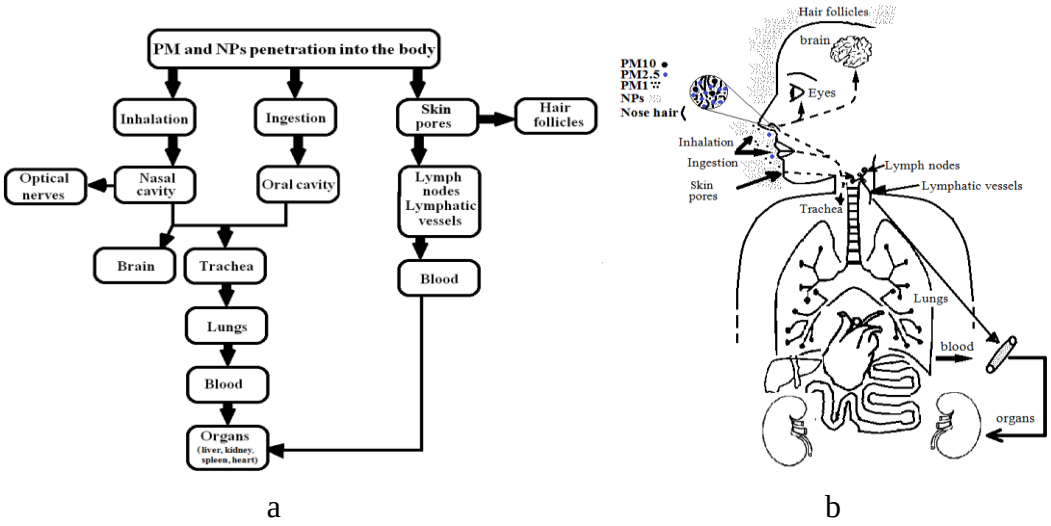

Fig. 1. Pathways of penetration of PM and NPs in the living body: a) representative scheme and b) transport in the body.

The main way of penetrating air emissions into the body is ***inhalation*** [18]. PM and NPs enter through the nasal cavity where the hair strands are the first barrier. Some of the PM is retained on these strands by passing only fine particles to the trachea [19]. The role of the trachea is to remove with the help of cilia the

particles that have managed to escape from the area of the nasal cavity back to the outside by enticing movements from bottom to top. Epithelial cells in the respiratory system that interact with inhaled nanoparticles signal their presence and trigger cellular defense pathways [20]. NPs penetrate the respiratory tree, infiltrate the circulatory system through the process of alveolar diffusion, deposit in the airways and induce various types of lung inflammation [21]. Most respiratory diseases occur as a result of the deposition of atmospheric emissions and their passage through the alveolar barrier. Metals such as nickel and copper are bound to the surface of PM and NPs, thus reducing the effectiveness of endothelial epithelial cells of blood vessels in the lungs and heart. Short-term exposure can cause ischemic heart disease, chronic lung obstruction [22], myocardial infarction, arrhythmias, high blood pressure, and congestive heart failure. Recently, the World Health Organization (WHO) reported that ischemic disease caused 36% of deaths due to global air pollution [23]. However, these PMs and NPs do not stop here and even attack the immune system. Due to their toxic composition and extremely small size, alveolar epithelial cells and alveolar macrophages that protect the respiratory tract become sensitive under their action. The accumulation in the alveolar region takes place through the air flow, thus damaging not only the lungs but also the other organs (kidneys, liver, spleen, heart) through the blood circulation. Adverse effects are observed through the dysfunction of the body which facilitates the appearance of the diseases mentioned above [24-28].

Exposure to NPs from air pollution can affect vision. The eyes are exposed through direct contact to air pollution resulting in irritation, discomfort, inflammation and the risk of certain diseases such as myopia, glaucoma, damage to the optic nerves and blindness [29, 30]. The elderly, children and people with eye diseases are most affected by air pollution. Exposure to NPs not only affects the eyes but is associated with mental health disorders because they manage to pass through the nasal mucosa and transcend the brain membrane systems known as the meninges [31]. The growing period of children is the most critical in the normal development of the brain. Exposure to NPs increases the risk of side effects such as decreased cognitive function, autism and over time neurodegenerative diseases such as dementia, Alzheimer's and Parkinson's may occur [32-34]. These situations often occur in large or developing metropolitan cities. Heavy traffic and population activities are the best example of the body's interaction with the resulting NPs and the association with the effects caused by exposure.

Ingestion occurs in two ways: *involuntary* when atmospheric emissions pass through the oral cavity. It often happens when there are conversations with a person next to you or when we talk at the mobile phone on the street where the

pollution exists due to road traffic and socio-industrial activities. Regarding the rural environment, the ingestion is due to agricultural activities. From this part of oral cavity, NPs reach the trachea, lungs, and the bloodstream through which it reaches the other organs.

Through *contaminated food and drinking water consumption*. NPs reach the gastrointestinal system where changes in intestinal cells occur due to oxidative stress. This action facilitates the interaction of NPs with the luminal environment of the intestine which leads to gastrointestinal disorders, inflammatory bowel effects, increased bacterial strains, increased risk of Crohn's disease and finally colon cancer. Under these conditions, daily activity is affected and unwanted changes occur [35, 36].

Another way of exposure is the ***pores of the skin.*** The skin represents the outer covering of the whole body and which has prominences in the form of small holes from where the hairs and wrinkles arise. NPs that can pass through the skin pores are so small that they enter through the hair follicles and sebaceous glands. It should be mentioned that in addition to the emissions from the air that can penetrate through the pores of the skin, there are also personal care and pharmaceutical products. These products are potentially harmful through frequent use and through the mixed constituents intended for external parts of the body. We mention in this category sprays, face and body creams, foundation, soaps, perfumes, lotions, shampoos, toothpaste, nail polishes [37, 38]. The literature shows that hair strands act as a mechanical force on nanoparticles pushing them as deep as possible into the hair follicles. When skin barriers are damaged, NPs can come into direct contact with the layers of keratinocytes, enhancing their bioavailability. In this situation NPs can generate genotoxic effects, oxidative stress with effects on DNA, blackheads that block the cleaning of pores resulting in acne. People sensitive to skin diseases such as dermatitis and eczema are most affected by exposure to NPs [39].

Penetration into the human body is easy and proven by the pathways in Figure 1. The circuit into body causes some of the nanoparticles to be partially metabolized, retained or eliminated. Definitive elimination from the body is not possible. The easiest method from eliminating deposited particles is by sneezing in the case of nanoparticles in the nasal cavity or by coughing in the case of nanoparticles stored at the extra thoracic level. For the other regions, elimination is more difficult because air particles follows the path of metabolism and can cause major damage over time.

Health is a key factor in being able to live properly, in an unpolluted environment and free of any foreign body. Nowadays, everything depends on us to be healthy, but unfortunately we avoid this. Nano dusts in the air mercilessly

attack living organisms, whether plants, animals or humans. Their action depends very much on the size, shape and concentration to which the living being is exposed, the crystallinity and functionality of the surface. Atmospheric nanoparticles cause multiple diseases but can overlap with other environmental conditions or social climates such as poverty related to inadequate nutrition. If the body's immunity is deficient, exposure will set in motion a condition that will become chronic over time and lead to slow death. All these effects are obtained from the professional work environment or from long-term exposures to a dusty environment. A proper diet, abundant in vitamins (fruits, vegetables, dairy) can increase the human body's resistance to the harmful actions of PM and NPs.

Association of PM with the new SARS-CoV-2 virus

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the name given to the 2019 novel coronavirus. SARS-CoV-2 is a new strain of coronavirus that has not been previously identified in humans. COVID-19 is the name given to the disease associated with this virus.

Public health has now become the most important concern of mankind. Given the new pandemic with COVID-19, an extremely virulent and dangerous disease, it has managed to destabilize the entire planet causing damage both socio-economically and health fields [40]. The factors that lead to the high mortality rate due to coronavirus are the already existing conditions (diabetes, hypertension, stroke) but also age [41]. Although this disease is new and under investigation, we must take into account that air pollution is a significant factor in the development of lethal diseases. The association of COVID-19 with air pollutants aggravates the situation in the public health system, and can be spread through atmospheric particles, saliva and nasal mucosa, smaller than 5 μm in diameter [42]. Of course, this approach needs to be deepened, it requires hard and long experimental work but it deserves the attention of the exploitation in order to stop a disaster [43]. Although, studies on this topic have shown that during the state of emergency in most countries there has been a decrease in PM pollution levels, which is an extremely good fact, the role of PM and of air pollution in the spreading of the virus are still urgent and crucial to be elucidated. Recently, it has been shown that the virus adheres to the PM which makes the virus very easily transmissible by air [43, 44]. Further, different studies have shown a correlation between PM2.5 and NO_2 with COVID-19 [45-48].

Nitrogen dioxide (NO_2) is produced naturally from biological degradation, volcanoes, oceans, vehicle evacuation and domestic heating [49]. NO_2 in vivo exposure, stimulates the release of *proinflammatory cytokines* (IL-8, TNF-α and IL-1β) in human lung epithelial cells [50, 51]. Thus, the exposure of human subjects to NO_2 led to increased infection with influenza virus A and the

appearance of inflammation of the upper respiratory tract. NO_2 may contribute to the appearance of inflammation and aggravate SARS-CoV-2-induced lung damage due to damage to immune cells [52]. Long-term exposure to NO_2 causes asthma, bronchitis, and allergic rhinitis, dermatological conditions because of direct action on the angiotensin-converting enzyme-2 (ACE 2) found in lung cells [53].

The mechanism of virus and air pollutants entry into the host cells through ACE2 receptors is given in Figure 2.

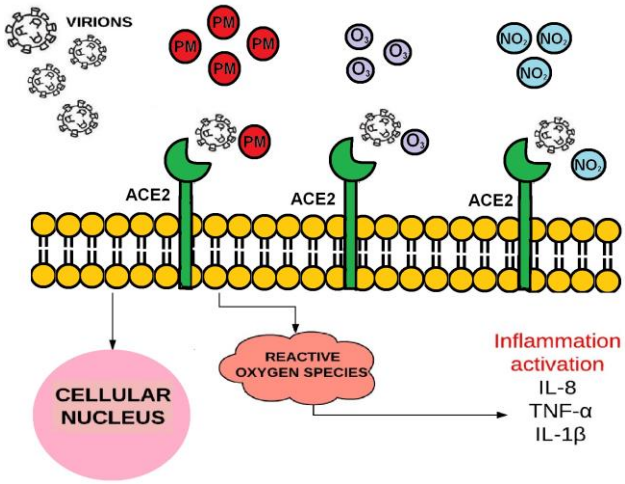

Fig. 2. The mechanism of viral and air contaminants entry via ACE2 receptors through the plasma membrane (i.e., lipid bilayer) into the human host cell.

Virus entry into human cells is initiated by the attachment of virions to ACE2 receptors and is followed by important conformational changes of viral proteins, and by the penetration through cellular membranes. The process is facilitated by air pollutants (e.g. PM, and various toxic compounds, like O_3 and NO_2) and ends with transfer of viral genomes inside the host cellular nucleus, causing the inflammation activation.

Angiotensin-converting enzyme-2 (ACE2) is a hormone that regulates blood pressure by acting directly on blood vessels that are in the lungs, as well as in endothelial cells or kidneys [52]. The receptor to which SARS-CoV-2 binds in lung cells is represented by this enzyme. Thus, exposure to NO_2 increases the ability of viral infection COVID-19 and the occurrence of lung complications [54, 55].

A study showed that the number of cases of COVID-19 was highest in London and the Midlands, where there is also the highest average annual concentration of

air pollutants. The finding provides the first evidence where SARS-CoV-2 deaths are associated with elevated levels of nitrogen dioxide [56, 57].

Recently, the association of PM with the new COVID-19 in 49 China cities was investigated and found that with a 10 $\mu g/m^3$ increase in PM2.5 and PM10 concentrations, the mortality rate with the new virus increased by 0.24% and 0.26%, respectively [45].

Another study, this time from Italy, showed that although the new virus is transmitted through bioaerosol droplets from person to person and through contaminated surfaces, it seems that urban pollution levels due to environmental factors (temperature, humidity) contribute significantly to increasing cases of COVID-19 infection [58]. It is also hypothesized that the warm season will not stop the spreading of the virus. Although we are vulnerable not only to the unknown SARS-CoV-2 virus, it is known that short or long term exposure to PM has led to chronic disease and even death.

American researchers evaluated air quality before and during the pandemic. This study was performed in the US for PM2.5 and NO_2. If in the period before the pandemic the data showed a decrease of the NO_2 value of 5.5%, during the pandemic a significant decrease of 25.5% was observed. In the case of PM2.5, the data before the pandemic showed a decrease of 3.75%, while during COVID-19 the decrease was 4.45% [59]. Another study found that a small 1 $\mu g/m^3$ increase in long-term exposure to PM2.5 resulted in the 11% increase in COVID-19 mortality [60].

A study on the role of environmental factors in accelerating the spreading of SARS-CoV-2 was conducted by Copat et al. in 2020 for PM10, PM2.5 and NO_2. They pointed out that air pollution affects the immune system which leads to vulnerability among the population and consequently to the biggest environmental cause for diseases and premature deaths. Through the data presented in their review, they highlighted that PM2.5 and NO_2 have a close correlation with COVID-19 compared to PM10. One explanation would be the inability of particles larger than 5 μm to reach alveolar cells [61]. Another studies show that the high concentration of PM10 was associated with a low incidence of COVID-19, due to its large diameter. The angiotensin-converting enzyme-2 is located in the alveolar cell type II which can only be reached if the diameter is less than 5 μm [55, 62].

In Spain, more precisely Madrid and Barcelona, during the state of emergency in March 2020, there was a significant decrease in NO_2 by 62% and 50%, respectively. The measurements were obtained from air quality monitoring stations and an improvement in air quality was observed by reducing traffic, closing non-essential activities and industries [63].

Regarding SO_2 a study by a group of researchers from India noticed a reduction in New Delhi from 9.9 $\mu g/m^3$ to 6.0 $\mu g/m^3$ and in Islamabad (Pakistan) from 120 $\mu g/m^3$ to 18.86 $\mu g/m^3$ during the state of emergency. They also studied O_3 but no critical changes were found. Therefore, these researchers conclude that such a large-scale emergency opens up new opportunities for formulating air and environmental quality control strategies in the future [64].

In Romania, more specifically in the Galati County, the effect of the state of emergency from March 23 to April 15, 2020 on NO_2 pollutant was investigated. The study's authors state that the decrease in NO_2 concentration is relatively small (10%) due to reduced road traffic. Although the city is quite small compared to other cities in Romania, the effect of lowering the NO_2 concentration is attributed to the restrictive measures imposed during COVID-19 by the authorities [65]. Regarding SO_2, in the Constanta port, the governmental measures taken during the emergency period positively affected the air quality due to the significant reduction of the traffic by 40%, the SO_2 concentration in the air decreasing by 30%. A conclusion of the study is that the state of emergency was beneficial for improving air quality. However, in case of a similar situation of re-imposing the state of emergency, it is necessary to perform new analyzes comparing in this way the daily values of the air pollutants [66].

However, the contamination of PM with viruses and bacteria (including COVID-19) has always led to a negative impact on public health, starting with the alteration of the immune system and continuing with aggressive changes on the organs of the living being. Under these conditions, exposure to air pollution associated with the new coronavirus leads to increased lethality of chronic diseases [67]. For a correct estimation of the impact on public health from the perspective of the association of air pollutants with COVID-19, additional epidemiological studies are absolutely necessary. These studies can accurately explore the interactions between particles and viruses in the air. Therefore, areas with high concentrations of pollution either indoors or outdoors will cause an increased rate of COVID-19 infection. There is an urgent need to implement preventive measures and resistance to the harmful actions of associating the new SARS-CoV-2 virus with PM in the air.

The impact of air pollutants (PM and NPs) on the human body

Maintaining the quality standards of the environment implies a health full of vitality, energy, joy, strength and courage. This good functioning is preserved as long as in nature, no destructive elements are introduced that endanger life. The importance of the air pollution debate is a delicate topic at the level of the entire planet, both from an environmental and public health point of view.

The impact of air pollutants on the living being largely depends on the nature of their origin (natural or anthropogenic), size, morphology, mode of exposure, buoyancy time and concentration. A study by the Global Burden Disease (GBD), conducted in 2015, found 4.2 million deaths from air pollution, especially in large cities [68, 69]. According to data from the literature and from environmental agents, PM has been found to be a varied source of chemical constituents including nitrates, sulfates, ozone, CO, street dust, silicates, volatile organic compounds, polycyclic aromatic hydrocarbons, bacteria, viruses, heavy metals. A statistic of the negative effects of these severe pollutants on the body is highlighted in Table 1 [70-80].

Table 1. The effects of air pollutants on the human body

Pollutant	***Impact on health***	***References***
PM	- effects on the nervous system - asthma, chronic obstructive pulmonary disease (COPD), lung failure, lung cancer, silicosis, tuberculosis - effects on the reproductive system - cardiovascular diseases (cardiac arrhythmias, heart attack, myocardial infarction) - irritation of the eyes, throat and nose - effects on mucociliary and macrophage activity - neurodegenerative disorders	[28, 70-78]
SO_2	- headache, anxiety - respiratory problems (facilitates bronchoconstriction, cough, affects the mucous membranes of the throat, nose and eyes) - cardiovascular diseases	[28, 70-74, 77]
NO_2	- effects on organs (liver, spleen) - effects on the circulatory system - respiratory problems (affects the mucous membrane of the	[70-74, 76]

	nose, eyes and throat, increases bronchial reactivity and susceptibility to infections) - tuberculosis	
O_3	- respiratory problems (inflammation of the mucous membrane of the respiratory tract, obstruction of the airways, damage to the epithelium covering the airways) - cardiovascular diseases - inflammation of the cells that cover the lungs, causes coughing, chest discomfort	[28, 70-73, 77]
CO	- effects on hemoglobin by blocking oxygen transport - effects on the fetus - causes headaches, nausea, vomiting, dizziness, weakness, loss of consciousness - tuberculosis	[71, 74, 76]
VOCs (volatile organic compounds)	- irritation of the nose, throat, eyes and mucous membrane - cancer - skin irritations - increased nasal congestion	[79]
Polycyclic aromatic hydrocarbons (PAH)	- cancer - mutations - affects the liver - Disruption of endocrine functions	[79, 80]

Assessing the diversity of diseases that air pollution causes to the living being, we must mention that short-term exposure will cause only minor symptoms in the respiratory system compared to long-term exposure that will produce severe side effects increasing the mortality rate. According to air quality standards, the most

vulnerable people are children, the elderly, those with chronic pre-existing diseases and pregnant women [80-83].

Exposure to PM produces oxidative stress, triggered by the activation of inflammatory cells. Such a study was performed on mice and it was found that alveolar macrophages begin to produce reactive oxygen species, nitrogen species and the cytokines TNF-α and IL-1. Tumor necrosis factor (TNF-α) is a protein used by the immune system in cell signaling and is one of the factors involved in the pathogenesis of chronic obstructive pulmonary disease. Interleukin 1 (IL-1) is an inflammatory cytokine having the biological function of regulating inflammation by controlling the immune system. PM10 and PM2.5 also produce reactive oxygen species (ROS), the main source of cellular organs (mitochondria and peroxisomes) that facilitate the onset of lung disease and asthma through either environmental toxins or daily diet. ROS is able to alter the structure of proteins and lipids, increase reactivity and airway secretions, decrease cholinesterase and endopeptinase activity. Thus, epidemiological evidence shows the consequences of exposure to PM2.5 by affecting the defense of the host's defense system with the development of asthma, chronic obstructive pulmonary disease (COPD) and infections [84-88].

In vivo studies were performed on short-term and long-term exposure to PM2.5. A group of researchers observede from experimental data that after a few days of exposure, hypothalamic inflammation occurs, fat mass increases and also increased slightly food intake [89]. Compared to long-term exposure, changes in neuropeptide expression occur, leptin sensitivity is affected, and hyperphagia occurs. Macrophage function is suppressed, lung self-cleaning is slowed and infections with P. aeruginosa, S. aureus, K. pneumoniae, S. pneumoniae increase significantly [69, 90].

In vitro studies have shown that PM2.5 penetrates the lung cell carcinoma (A549) increasing the risk of infection with M. tuberculosis, disrupts the airway epithelium and disrupts the defense system against pathogens by increasing the risk of P. aeruginosa infections. It has also been observed that the adhesion of S. pneumoniae on the PM2.5 surface develop respiratory infection by binding to primary alveolar macrophages and tracheal epithelial cells [69]. Adherence is encouraged by oxidative stress and the receptor for platelet activating factor [91].

Another group of Chinese investigators verified the effects of PM2.5 in both the short and long term from exposure by including participants over the age of 18 in the study for one year. The results showed a significant association of air pollution with PM2.5 and the risk of acute nasopharyngitis in both cases of short and long term exposure. This study recommended that older people avoid short-term exposures and young people long-term exposures [92]. Due to its large

surface area and very small size, PM2.5 has a rich arsenal of toxic substances that pass through the gills and alveoli of the lungs until they reach the circulatory system through the gas-blood barrier. Thus, epidemiological studies following research have shown that due to PM2.5 increased the number of hospitalizations for acute respiratory infections and susceptibility to lung infections [69].

As for nanoparticles, they are recognized for their ability to combine with potentially hazardous elements, either from primary sources (construction, mining, paving, fire) or from secondary sources generated directly in the air following the interaction of pollutants (gaseous contaminants, exhaust fumes, acids). Health consequences are observed through symptoms that cause local and systemic lung inflammation, oxidative stress, adverse reactions on the brain and metabolism, brain delay, autophagy, cancer [93, 94]. Also, polycyclic aromatic hydrocarbons (PAH) from exhaust gases diffuse easily through cell membranes, thus modifying DNA, lipids and proteins. Research on rodents has revealed that inhaled NPs are directed from the nasal cavity into the brain resulting in neurodegenerative changes such as synaptic dysfunction and inflammatory responses in vivo and in vitro. NPs can also induce the production of glial tumor necrosis factor alpha (TNFα) [95].

An important source of NPs with high development potential in the world is the design of nanomaterials for different industries. So nanotechnology has now become an indispensable source for the manufacture of consumer products [96]. Their performance in the field of research is due to the physico-chemical, mechanical, optical characteristics, structure, reactivity, strength and dimensions in the range 1-100 nm which is certified by the European Commission, International Organization for Standardization (ISO), Environmental Protection Agency (EPA) and the US Food and Drug Administration (USFDA) [97, 98].

Specialist studies have shown that NPs enter the body through inhalation, ingestion and skin pores thus translocating into organs and tissues. In terms of toxicity, NPs can have adverse effects on the environment and public health. An example are *TiO_2 NPs* used in personal care products, medicine, agriculture, construction, food industry. Exposure to these NPs occurs during manufacture and use in a wide range of fields. Thus, the body can trigger the production of oxidative stress, reactive oxygen species (ROS), metabolic disorders, apoptosis, chromosomal instability, inflammation, genotoxicity. In vivo and in vitro studies confirm the presence of TiO_2 in organs (lungs, spleen, liver, heart, digestive tract) which disrupts the proper functioning of lipids and glucose [99-101].

Silica NPs are widely produced due to their excellent biocompatibility and stability in the biomedical field [102, 103]. Being a product with excellent capabilities in medical applications it should be specified that exposure to

crystalline silica nanoparticles can cause lung diseases such as silicosis, emphysema, tuberculosis and cancer. Epidemiological studies in rats have also shown that amorphous silica NPs have adverse effects on macrophages and lung epithelial cells. The action on the body can also induce neurodegenerative changes and ataxias [104-106]. Therefore, once they enter the living system, these NPs work on tissues, cells, organs and bloodstream, resulting in severe pathologies.

Emissions of SO_x, NO_x, CO from traffic, burning of fossil fuels, incomplete combustion processes and other sources, react with particles in the air contributing to the deterioration of air quality. The fineness of the particles is classified as dangerous and toxic to the respiratory system. The immune system is intensely exposed to these harmful pollutants becoming sensitive and unable to act against them. These pollutants affect the environment by producing strong acids (H_2SO_4 and HNO_3) and thus acid rain [10] which through food consumption can affect the body. SO_x causes destabilization of the heartbeat, headache, cough, skin cancer and NO_x causes respiratory failure, effects on the circulatory system and organs. Accumulated stress in the body causes DNA changes resulting in abnormalities at the molecular level. In other words, the body becomes the host and is affected in all respects by inducing respiratory, lung, cardiovascular, cancer and death diseases [107, 108].

Exposure to polycyclic aromatic hydrocarbons (PAHs) is due to the burning of fossil and industrial fuels, smoking, fires and food consumption. It consists of a number of compounds, the best known of which is BaP (benzo [a] pyrene). Inhalation of PAH is done by passive diffusion, reaches the lung cell membranes and develops the formation of lung cancer and DNA modification [109, 110].

PM and NPs have customized properties that can interact with the living system components. They act as foreign materials intentionally introduced into the environment and implicitly aggravate public health through various pathologies such as chronic obstructive pulmonary disease (COPD) and asthma. Both conditions are characterized by inflammation and irritation of the airways, allergies that manifest as early forms of tearing, rhinorrhea. Of course, they are not the only pathologies due to pollution, but they are the main ones in terms of interaction with the respiratory tract and lungs. The theoretical study on the current state of the issue in this review highlighted the risks associated with PM and NPs. Each type of particle acts differently on the limbs it attacks and this is due to the complex properties it exerts in its interactions.

Nanoscale interaction of NPs with the biological membrane

Nanoparticles are considered advanced nanostructured materials obtained from the progress of nanotechnology and are of interest in the biomedical field being easily applicable in medicine and biology. The literature has highlighted a

wide range of NPs from vast fields of research due to their size, they interact with the biological membrane, the extracellular matrix, proteins, lipids, amino acids, offering a wide range of applications. Currently, although there are studies on the interaction with the living system, the mechanisms of action and the negative effects on the biological system must be elucidated. Thus, in Figure 3, is illustrated a series of beneficial activities for public health but also toxic effects that can destabilize the functioning of the biological system as a result of interactions.

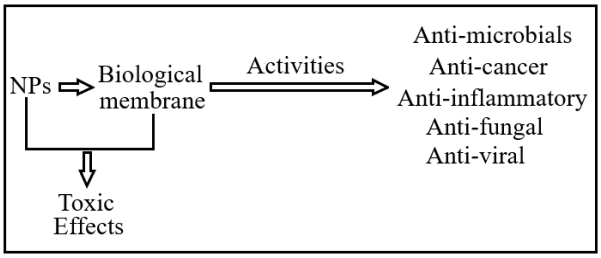

Fig. 3. The interaction of NPs with the biological membrane; leading to various biological activities and toxic effects.

NPs with beneficial health activities are GNPs and SNPs, studied in our research team and showing anti-microbial [111-113], anti-cancer [114-116], anti-inflammatory [117, 118], anti-fungal [119] and anti-viral [120, 121] properties. They can also be functionalized with various biomolecules (vancomycin, resveratrol, doxorubicin, anesthetics) thus showing synergistic effects on bacteria, tumor cells and other pathologies [122-130]. Due to the interest of researchers GNPs and SNPs can be arranged through self-assemblies using the Langmuir-Blodgett (LBT) technique. This technique succeeded in opening new opportunities to investigate metallic nanoparticles self-assembled at the air-water interface so that the conjugations of metallic NPs with biomolecules becomes a new tools to evaluate their mechanism of action when are used as drugs carrier at the target site of action [131-135].

The ability of NPs to bind to biological membrane cells has been and is being discussed globally in the field of colloid and interface science. In this sense, self-assembled LB and multi-layer LB cell membranes were used as membrane models as the monolayers at air-water and at oil-water interface [136-141]. Physically, chemically and biologically, nanostructured multifunctional materials have been characterized, such as membrane lipids, lecithin, galactolipids [142-146], collagen [147-150], fatty acids [151-154], stearic acid [155-161], phospholipids [162-166], proteins [167, 168], carotenoid pigments [169-177], cholesterol [178, 179], drugs [180], antioxidants [181-183], hydroxyapatite [184-195] all having applications in nano and biotechnologies.

Undoubtedly, the interaction of NPs with the biological membrane also highlights harmful effects. Epidemiological evaluation of toxicity shows that the interaction of NPs with the lungs leads to a reduction in the effectiveness of lung surfactant metabolism [196]. Pulmonary surfactant is the barrier that defends the surface of the alveolar lumen, and NPs are interacting in the first phase with pulmonary surfactants and then with epithelial cells [197]. Basic pulmonary surfactant models such as phospholipids (e.g., dipalmitoyl phosphatidyl choline: DPPC, dimyristoyl phosphatidyl choline DMPC) can be modified by NPs in a concentration-dependent manner; this means that the effects are specific to the type of material tested [198]. This review showed through this study that the size and loading of the NPs surface inhibits the functioning of the living system by damaging the protective barriers of tissues and organs. The investigation of these air pollutants on the biological membrane brings fundamental knowledge about the entry pathways of NPs, the binding power of harmful substances and their reactivity in different environmental conditions. In the current context of the pandemic, the attack of coronavirus (SARS-CoV-2) on the respiratory tract and lung function is much faster and more harmful, the biological membrane being already obstructed by the interaction with NPs. In this sense, the rate of illness and mortality is expected to increase.

Combating air pollution with PM and NPs is absolutely necessary in order to reduce unwanted impact to the public health. Although there are a number of countermeasures that depend on the season and the source of pollution, a natural method capable of improving air quality in urban areas is phytoremediation. This ensures better living conditions and a proper climate that brings public health benefits [199, 200]. Awareness of the negative impact created by pollutants on the environment, can improve legislative strategies and the quality of respiratory and lung health.

The ACE2 is the receptor for the SARS-CoV-2 spike protein and is involved in virus internalization into the host cells, more exactly in alveolar type 2 cells in the lungs that produce inflammation. Chronic exposure to PM2.5 is known to increase epithelial and endothelial ACE2 expression. When the SARS-CoV-2 virus binds to epithelial cell receptors, ACE2 can stimulate the release of proinflammatory cytokines in the systemic circulation. The hypothesis of virions adsorption to PM has not been sufficiently tested and the effects of exposure to air pollutants associated with SARS-CoV-2 are still unclear [201-203].

Conclusions

The atmosphere is the gaseous shell of the planet and is characterized by physico-chemical parameters (density, pressure, humidity, temperature) that make it possible to survive on earth. Changing the operating parameters by introducing

foreign components proves to be toxic and dangerous both for the environment and for public health. Air pollution research is a topical area and needs to be investigated in order to improve the quality of life.

Atmospheric pollution with PM and NPs can have natural origins (volcanic eruptions, sea salt, pollen, spores, mold, forest fires, rock disintegration) and anthropogenic (road traffic, burning fossil fuels, waste incineration, burning of hydrocarbons). Most PM and NPs in the air are the result of socio-industrial activities that are emitted directly into the atmosphere. Also they can form as a result of chemical reactions with other particles from air.

The chemical composition, size, reactivity and morphology of particles is variable from one area to another for which the interaction with the living being is different. Approaching such a study from an epidemiological and toxicological point of view will highlight the negative impact on the respiratory tract and lungs. Their characterization is essential in order to develop strategies for environmental protection and implicitly for health.

The present review highlighted the ways of penetration of PM and NPs in the body (inhalation, ingestion and skin pores) exposing a series of effects generated on the human body (skin diseases, respiratory diseases, lung diseases, cardiovascular diseases, neurodegenerative diseases). It has also been described that the elderly, children, pregnant women and people with pre-existing conditions should avoid both short-term and long-term exposures.

The interaction of PM and NPs with the biological membrane, although not yet fully elucidated, has highlighted the ability of NPs to bind to biological membrane, their interaction with cells is discussed globally in the field of colloid and interface science. Models for mono- and multi-layer membrane assembled using the Langmuir-Blodgett technique was used at the air-water and oil-water interfaces. There have been beneficial effects of some NPs through antimicrobial, anti-viral, anti-inflammatory and anti-cancer activities but also the harmful effects were identified by which NPs lead to reduced effectiveness of lung surfactant metabolism.

This review also addressed the association of NPs with the new coronavirus (SARS-CoV-2) which reveals through specialized studies that areas with high concentrations of pollutants either indoors or outdoors will cause an increased rate of COVID-19 infection. The problem is currently under investigation, which requires time for a more detailed investigation in order to conclude a concrete association with air pollutants.

Air quality is constantly improving due to environmental legislation, protection rules, coercion by the European Commission to comply with pollution rules, educating the population and awareness of the negative impact on health,

techniques currently used to reduce pollution (phytoremediation, maintenance existing infrastructure and asphalting of unpaved roads). Respecting the rules and good intentions of the population could lead to ensuring good living conditions so that the rate of illness and death decreases significantly.

Acknowledgment

This work was supported by grants of the Ministry of Research, Innovation and Digitization, ***CNCS/CCCDI-UEFISCDI***, project number 186 and 481, within *PNCDI III*.

POPA Roxana Cristina, MD, gratefully thanks the doctoral Program of the Doctoral School of Chemistry, the Institute of Doctoral Studies, from Babes-Bolyai University of Cluj-Napoca, Romania and the Research Center of Physical Chemistry for provided support and strategic tools, top research instruments and cutting-edge technology for the PhD research project at various stages. POPA Roxana Cristina also thanks the supervisor, Univ. Prof. Dr. Maria TOMOAIA-COTISEL, Founder and Director of the Research Center of Physical Chemistry for providing excellent guidance, encouragement and strong scientific support for her doctoral research activity.

Notations and/or **Abbreviations**

WHO - World Health Organization

GBD - Global Burden Disease

VOCs - Volatile Organic Compounds

PAH - Polycyclic Aromatic Hydrocarbons

TNFα - Tumor Necrosis Factor

IL 1 – Interleukin 1

ROS - Reactive Oxygen Species

COPD - Chronic Obstructive Pulmonary Disease

ISO - International Organization for Standardization

EPA - Environmental Protection Agency

USFDA - US Food and Drug Administration

COVID-19 - coronavirus disease
SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2
BaP - benzo [a] pyrene
GNPs - Gold Nanoparticles

SNPs - Silver Nanoparticles

ACE2 - Angiotensin-converting enzyme-2

RAS - renin-angiotensin system

DPPC - dipalmitoyl phosphatidyl choline

DMPC - dimyristoyl phosphatidyl choline

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