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Allergens, Air Pollutants and Immune System Function in the Era of Global Warming

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1. Introduction

Nowadays, almost half of the world's population lives in or near areas where the quality of air is poor. Rapid changes in the environment related to the "industrial revolution" have changed the earth within almost no time. These civilization changes are usually positive, as they lead to technological advancement, raising living standards, providing better health care and hygiene. They are however accompanied by unforeseeable climatic changes and negative health effects, which result from progressive contamination of the biosphere, as well as excessive exposure to toxins and allergens. They, in turn, lead to a growing number of immune system dysfunctions or even deaths in animals and humans.

It is estimated that in the 20th century, only around 100,000 chemical substances were introduced. However, the pace at which new ones are being introduced is still growing. In 2009, 50 million synthesized chemical compounds were entered into the international register, "The world's largest substance database" and of that number, 143,000 compounds were used for industrial purposes. At present, as it has been recently updated (04 November 2011), the number of the registered compounds is now 63, 839, 600 which means an increase of more than 20% within less than two years [59]. It is a fact that the air in urban city agglomerations is contaminated with hazardous compounds which appear as a result of the process of incomplete burning of minerals used in transport, power and other industries. Some of them exacerbate the greenhouse effect and cause disorders in the immune system. Additionally, we should not neglect the widespread pollution of rural areas. Pollution also brings about disorders in the immune system in humans, domestic animals as well as wild animals. Although the concentration of certain chemical substances is monitored in the air, water and food, some studies have shown that the influence of the concentration on dysfunctions of immune system in an individual is very complex and often difficult to explain. When the homeostasis of the immune system is disturbed it is difficult to treat such cases.

The immune system is a highly complicated, even intelligent, system with a characteristic hierarchy. Studies show that the system often has difficulty in adapting to environmental changes. More and more immune pathologies are appearing. They start with immunosupression, immunomodulation and finish with autoagression and allergy. The reasons for these phenomena are still being examined. Epidemiological, clinical, as well as toxicological, examinations conducted on humans and animals are the grounds for evaluation of health effects resulting from environmental pollution. The analysis of factors

related to local and global environmental changes, particularly the toxicology of the urban environment, which might affect the proper functioning of the immune system is highly important from the point of view of public health. It is known already that environmental toxins can lead to reduced resistance of the epithelium and facilitate the contact of inhalatory allergens with the "network" of dendritic cells. The activation of these cells by toxic compounds make the allergens more recognizable. The exposure to the factors might lead to oxidative stress through the production of reactive oxygen (ROS) and nitrogen species (RNS) at an amount which cell defensive mechanisms cannot manage.

Environmental toxins, depending on the dose, can cause permanent changes, including epigenetic ones. Recently, the clinical evaluation of immune system dysfunctions has been thoroughly analysed; the genetic and environmental aspects are taken into consideration, as well as any climatic changes which might lead to an increase in the allergogenic potential of natural organic compounds that might directly affect the immune system [98]. All these factors and related compounds are potent. Their health implications might be unforeseeable, instant, long-term, irreversible or permanent. The aim of the study is a review of modern environmental toxins, their relationship to the process of global warming, the appearance of disturbances in the immune system as well as chronic inflammatory diseases of the respiratory system.

2. Classification of air pollutants

Air pollutants are usually classified as natural and anthropogenic. Another classification also takes the environment into consideration.

2.1 Natural pollutants

Natural pollutants – geological (e.g. volcanic ash emission, fires, emission of minerals coming from soil erosion). On the European scale, the pollution is monitored with satellite data from the UE MACC 2010 international research project. The European database for biogenic pollution (from 35 countries in Europe): pollen and fungal spores, can be found on http://www.polleninfo.org/.

2.2 Anthropogenic pollutants

Anthropogenic pollutants – chemical compounds which are produced as a result of human activity. They appear in industrial and metallurgical technological processes; they are combustion products of fossil fuels, dust and aerosols. The last category comprises pollutants which pose a health hazard for a man - NO_x O_3, SO_2, CO, nicotine smoke, hydrocarbons, lead, chromium, particulate matter (PM), including nanoparticles. There has been a rapid increase in the number of reports demonstrating a close relationship between the exposure to anthropogenic substances and disorders of the immune, respiratory and cardiovascular systems or even a growing number of deaths. Findings show that poor air quality results in dysfunctions of the immune system. They, in turn, lead to the poverty of people inhabiting the particular region [105,118]. The classification of pollutants is also based on the number of particles in the air, their origin and state of aggregation, while a further classification concerns the place where the pollutants are measured e.g. city/rural environment, air inside/outside a building. This study aims at presenting the influence of particular toxins on human health and we try to give a detailed description of those toxins one by one.

2.3 Dirty dozen: Examples of compounds which heavily pollute the environment and cause immune pathologies

The Environmental Protection Act and directives issued by the European Parliament and the European Council as of 21 May 2008 provide the necessity of constant monitoring of air and 12 of its components which pose a health hazard:

- nitrogen dioxide NO_2,
- sulfur dioxide SO_2
- carbon monoxide CO,
- benzene C_6H_6,
- ozone O_3,
- particulate matter PM_{10},
- lead Pb in PM_{10}
- arsenic As in PM_{10},
- cadmium Cd in PM_{10},
- nickel Ni in PM_{10},
- benzopyrene in PM_{10},
- particulate matter $PM_{2,5}$.

According to the provisions of the European Union, this act must enforced in all member states and its established regulations are required to be respected by cities with populations above 100,000 [37].

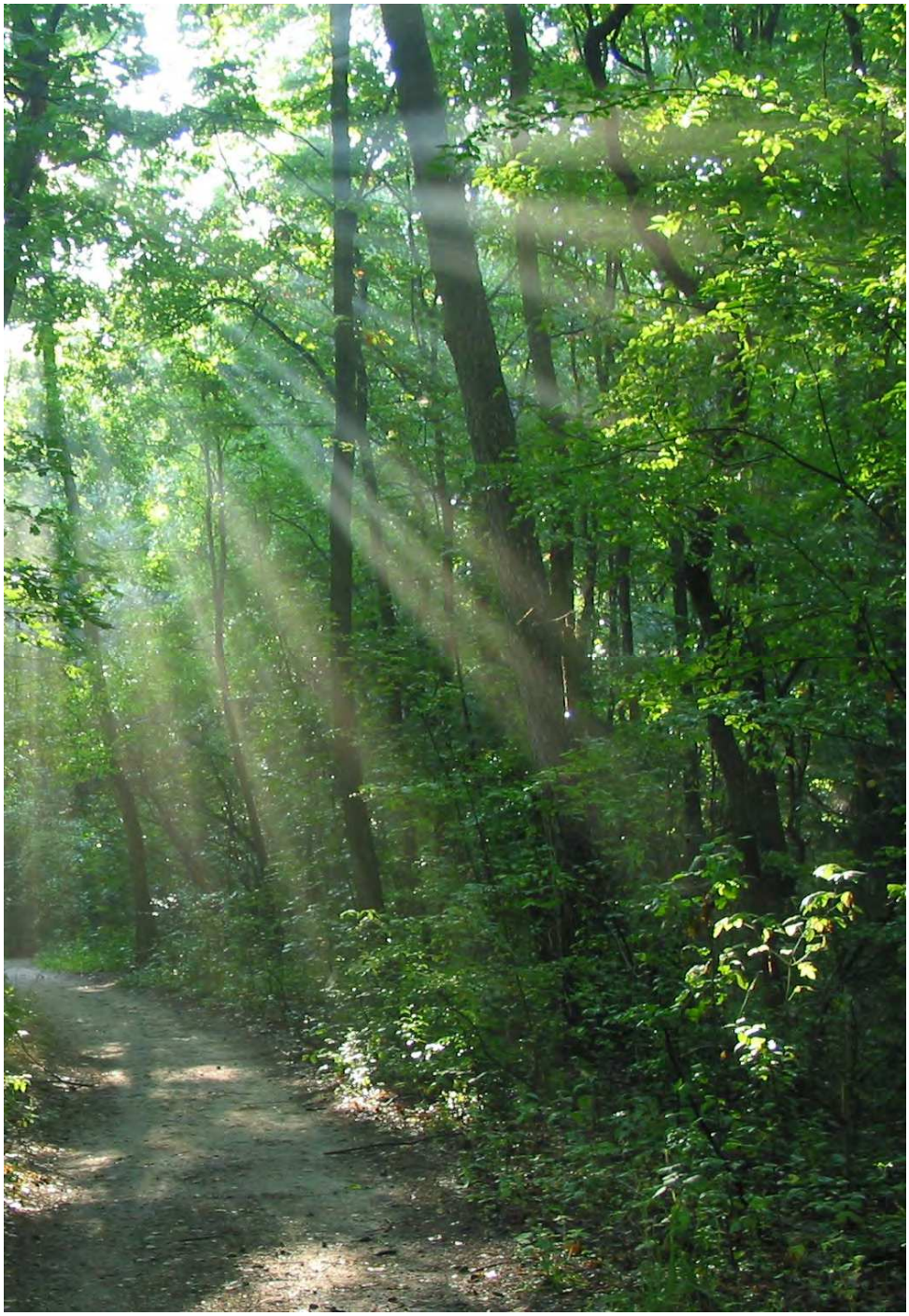
2.4 Urban outdoor pollution

Large cities are spread all over the world. In Europe, around 75% of the population live in cities. Therefore, the majority of scientific research on the topic of air pollution is performed in cities. The pace of migration from rural areas to cities is still fast. Unfortunately, city dwellers pay a huge price for living in large agglomerations where even breathing puts their life at risk. The air in major cities contains over 700 substances, both organic and inorganic compounds, as well as metals (e.g. lead, cadmium, manganese, mercury) and their compounds with other stable inorganic and organic substances, including DEP, soot, dust, smoke, dioxins, metals, polycyclic aromatic hydrocarbons (PAHs) – pyrenes, benzoapyrenes, dibenzofurans, polychloro aromatic hydrocarbons (VOC), fungal and pollen allergens and many others.

In polluted city environments, there is a deficiency of bacterial flora with probiotic and saprophytic properties (e.g. bifidobacterium, lactobacillus) and so the inhabitants are exposed to pathogenic microorganisms (e.g. Staphylococcus ureus, Candida albicans) [86]. It has also been confirmed that dust collected in city areas is characterized by higher oxidative activity, mainly because of the presence of metal ions $Fe3^{+.}$ In healthy people a typical concentration of dust (< 0.2 ppm) usually causes reversible effects such as irritation of the mucous membrane in the conjunctiva and upper respiratory tract.

2.5 Rural outdoor pollution

Air quality in rural areas is much less frequently monitored. Intensive agricultural development and other industries contribute to progressing soil and water pollution with the remnants of fertilizers and pesticides, which impoverishes soil and causes wood atrophy (Figure 1). In water reservoirs, algae bloom, block access to oxygen and cause eutrophication



Fot. Agnieszka Wojciechowska

Fig. 1. The effects of plant vegetation in unpolluted (Łódź, Arurówek) and polluted (Krzewo) areas in central Poland.

of water ecosystems. The agricultural industry also contributes to the excessive emission of nitrogen compounds; NH_3 and NH_4^+ ions have been used on a huge scale in artificial fertilizers since the 1st half of the 20th century. Nitrogen compounds and other substances coming from rural areas are bound by PM particles and often transported over longer distances by acid rain. Many compounds which are found in weed-killing agents may irritate the respiratory system and even block receptors for hormones or neurotransmitters; many pesticides are inhibitors of acetylcholinesterase. They negatively influence the homeostasis of the body and its immune system. Pesticides and toxic herbicides may also have immunotoxic and immunosuppressive properties. They can act by causing deactivation of lysozyme, an important protective factor against pathogenic Gram(+) bacteria present in saliva, tears, secretion of mucosa and body fluids in phagocytes [20]. On the level of adapted immunity, they can act by, among other things, inhibiting lines of T CD4(+), CD25(+)lymphocytes and T reg lymphocytes [30].

2.6 Indoor pollution

Poor air quality inside a building might constitute a serious environmental threat [41]. It has been confirmed that air pollution inside buildings is usually 2 - 5 or even 100 times higher than outside [62]. Interestingly, not only pollutants coming from outside are responsible; pollen, house-dust allergens such as mite allergens and cockroach allergens, as well as fungal spores, animals, household cleaning products, building materials, air fresheners, naphthaline and even dry-cleaned clothes also exert an allergenic effect [40]. House owners are also threatened with breathing fumes emitted during the process of burning traditional biofuels, such as gas, coal and wood, as well as highly toxic nicotine smoke, which contains more than 6000 toxins. One such component of cigarette smoke is nitrogen oxides, whose level ranges between 200 mg/m^3 and 650 mg/m^3 [147]. The WHO defines the 1-h limit value of 200μg NO_2/m^3 air. Due to their poor water solubility, the site of immunotoxicity of nitric oxides is the upper respiratory tract. The unfavorable situation inside buildings could be improved quite easily. For example, the use of chemical products could be reduced or the building occupants could stop smoking nicotine, since the filtration of air polluted with nicotine smoke is hardly effective [22].

Another world concern is pollution with bisphenol or tributyltin (TBT), compounds which can be found in house dust, as well as outside, and which can seriously impair the immune system in humans and animals.

Bisphenols (PBA, PBC) belong to a group of extremely dangerous toxic indoor compounds which have been in use for more than 50 years. Bisphenols can be found in many everyday products made of polycarbonate. Exposure to bisphenols is hazardous even in intrauterine life. Bisphenols have been identified in the blood of infants whose mothers used simple devices for recycling domestic waste while pregnant; they were exposed to polychlorinated biphenols (PBC) by breathing them in. The infants' birth weight was lower and their Apgar scores were worse [146]. The list of sources of biphenols is long. The compounds accumulate in house dust, which is highly dangerous for children. They can be found in commonly used plastic objects such as bottles for babies (although the production of bottles containing BPA in EU countries was banned in March 2011, and the import and sale of such bottles was banned in June 2011), plastic bottles for milk and drinks, kitchen utensils, wrapping food

foil, dental fillings, dentures, dental bridges, food and medicine packaging, as well as plastic elements within various medical devices such as inhalers, dialyzers, pacemakers, contact lenses and protective masks. They are also components of paper and are found in fire retardant agents in furniture and fabrics as well as in electric cables.

Bisphenol easily penetrates the skin, air passages and the alimentary tract. It can induce dangerous epigenetic changes in reproductive cells, disturbing chromosome division (aneuloplodia) thus potentially leading to Down syndrome. After heating or sterilizing these articles (e.g. bottles for babies) polycarbonates are slowly degraded and, as a consequence, bisphenol molecues are released dozens of times faster. Due to the similarity of PBA molecues to estrogens, these compounds induce many hormonal disturbances, mainly in the thyroid and pituitary gland; they also infertility, neoplastic diseases , diabetes, obesity as well as have neurotoxic properties [125].

Due to their high toxicity, tributyltins (TBT) are also regarded as some of the most dangerous substances polluting the indoor environment. TBT have been found in the air inside many public buildings and private houses [97]. Many analyses have confirmed their immunosuppressive character, which might lead to impairment of anti-infectious immunity and development of neoplasms. Despite this, TBT have been widely used in agriculture and industry since the 1960s. Nowadays they can be found in plastics, herbicides, household cleaning agents and building materials despite a considerable body of alarming information concerning their negative effects. They are in recycled products and their production has not been banned, yet. They are used for conserving wooden objects, hulls in ships, in textiles, plastic products, fungicidal, insecticidal and bactericidal agents, commercial catalysts and even toiletries, especially in antibacterial additives for washing liquids and soaps, pampers diapers and toys for children [74]**.** These toxins have also been traced in many alimentary products, even in the milk of breastfeeding mothers. Toxicologists warn against using plastic boxes, toys and other products, even those which were permitted to be sold by the FDA, because of their potential effect on cell metabolism. By disturbing endogenic steroid hormones and modifying the activity of many drugs, they induce irritation of respiratory passages, skin and eyes, and have neurotoxic properties [133]. It has been confirmed that TBTs activate peroxisome proliferator-activated receptors (PPARs), present on cells, which might lead to metabolic disorders, upset the lipid balance and as a consequence, lead to diabetes and obesity [29]. Nevertheless, there are hopes that recently isolated bacterial strains (class Bacilli and c-Proteobacteria) might play a role in the biodegradation of TBT [4].

2.7 Air Quality Index (AQI)

In most countries all over the world, the level of air pollution is constantly monitored. However, for many people, the data is inaccessible or cannot be understood. In American countries there is one general air pollution indicator called the Air Quality Index (AQI) [60], thanks to which, it is possible to provide a daily practical and yet complex evaluation of many pollutants on the American continent and show to what extent air quality might have a negative influence on health. The AQI values are presented on a six-grade scale. In European countries there are initiatives to introduce a uniform index evaluating air quality which might improve the system of sending information and warnings. The levels of EPA Air Quality Index and their relationship with oxidative stress biomarkers in epithelial cells are shown in figure 2.

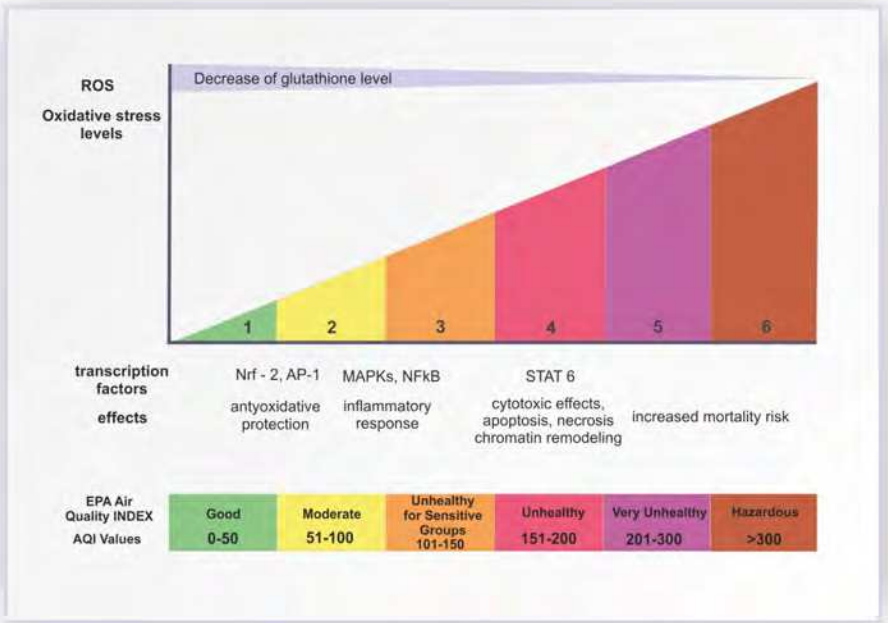


Fig. 2. Levels of oxidative stress biomarkers in epithelial cells and their relationship with the EPA Air Quality Index. It has been developed on the basis of the "Air Quality Index (AQI) - A Guide to Air Quality and Your Health" http://www.airnow.gov/index.cfm?action=aqibasics.aqi, and Xiao GG, Wang M, Li N, Loo JA, Nel AE. Use of proteomics to demonstrate a hierarchical oxidative stress response to diesel exhaust particle chemicals in a macrophage cell line. J Biol Chem. 2003;12;278:50781-90.

2.8 Allergens and environmental toxins

A great number of atmospheric aerosols are of biological character. It has been estimated that bioaerosol constitutes 5 – 10% of the total volume of PM [100]. Plant pollen and fungal spores are dominant in rural areas rather than in cities. However, city inhabitants more frequently suffer from pollen allergy [95]. According to scientific findings, the main factor favouring pollen allergy might be oxidative stress connected with the synthesis of NADPH endogenous oxidase in pollen grains such as those of birch or ambrosia, and air pollution of oxidative character. They can have a negative, pro-oxidative influence on cells of the epithelium of the respiratory tract, activation of dendritic cells and stimulation of pro-inflammatory processes which might contribute to the development of the allergy [113,5]. The evaluation of the dose-response relationship between the exposure to pollen and allergy symptoms is unclear. An interesting study was performed by scientists in Basel, Switzerland in which they gathered a database on the levels of birch and grass as well as the incidence of allergy over a period of 39 years. It concluded that within 20 years (from 1969 to 1990) with the increase in the level of pollen, there was an increase in the incidence of hay

fever and allergy to birch and grass pollens. In the two subsequent decades (from 1991 to 2007) scientists observed the decrease in pollen of these taxons, which was accompanied by a decrease in the incidence of allergy [45]. Other experiments have not shown a dose-response relationship between the sIgE level in serum and exacerbation of clinical symptoms induced by Timothy pollen [65]. It should be remembered that environmental allergens are most often the proteins of living organisms sensitive to changes in the natural environment, such as temperature, osmolarity, humidity, pH and exposure to toxins. Modern methods of molecular research facilitate introducing detailed patterns of environmental stress response (ESR) caused by environmental pollution; not only in terms of genetics, proteomics and kinetics of their synthesis but also in terms of the virulence/allergenicity of proteins, as well as the response of the immune system to synthesized compounds. The synthesis of co called pathogenesis-related proteins (PRS), which might be both allergens and toxins, is one of the forms of plant and fungal spore response to air pollution.

2.9 Pollen allergens and environmental pollutants

Plants are considered to be highly efficient, ecological air filters whose filtering capacity grows with the growing level of pollutants. They are able to absorb and accumulate magnetic nanomolecules (Fe_3O_4) [151] and even 97% of toxic VOCs (volatile organic compounds) from the atmosphere [72]. Rarely are the potential consequences for flora, fauna and a human considered. We already know that air pollution absorbed from the atmosphere contributes to the growth, development and yielding of plants. They have a toxic influence on generative tissues and decrease the production of plant pollens; for example, herbicides commonly used for killing weeds inhibit the production of pollens in arable crop [36].

Pollen grains are too large to get to the lower airways and the symptoms of allergic reaction depend on allergens emitted after the destruction of the pollen exine. It has been concluded that gas pollutants, found in PM, react with the hydrocarbons of the cell wall leading to the modification of its structure and changes in the shape of the pollen grain, which facilitates the release of allergenic proteins. Sometimes, under the influence of these changes, plants produce a greater number of grains but of smaller size. They can also penetrate the plant tissues and interfere with their physiological processes, the course of photosynthesis and the cell metabolic pathway. They induce some damage to cells and mutations. For example, upon penetrating the cell, SO_2 can react with water and become sulfuric acid, which inhibits the process of photosynthesis and damages cells [115].

Pollen allergens can remain in the air for as long as for a few weeks and join many pollutants. The presence of aeroallergens/air pollutants interactions appears to increase the morbidity from aeroallergens, but immunomodulation mechanisms are not clear. It is possible that allergens interact with environmental pollutants to increase their interactive effects (figure 3). Microscopic analysis showed that in a polluted environment, the exine (outer layer of the pollen) thinner, distorted and more susceptible to breaks, which favours the emission of allergens [26]. Also allergens emitted from pollen grains can change their properties under the influence of chemical substances [115]. It was confirmed that O_3 induces changes in intracellular signal transduction, which leads to changes in gene expression and changes in the structure of allergen proteins. Air pollution might also induce post-translational modifications of allergenic proteins. Chehregani et al. [25] confrimed that after 5 to 10 days' exposure to Diesel's particles (DEP) there was an increase in allergenic

potential of Lilium martagon pollen grains; immunoblotting subsequently confirmed the existence of modified or new protein (35 kD), which reacted with IgE antibodies of sensitized animals. Bommel at al. [18] stated that pyrene – an important component of DEP can aggravate an allergy by the induction of IL4 production. Exposure of human nasal epithelium to DEP and allergens (in vivo) contributed to a decrease in the IFNα and an increase in Th2 cytokines [135]. DEP particles can also act as allergic carriers, which intensify the presentation process by antigen presenting cells (APC) [66]. DEP particles can also induce epigenetic changes and in that way stimulate Th2 response, as confirmed by in vivo research [93]. The destruction of the exine by environmental toxins favours the release of

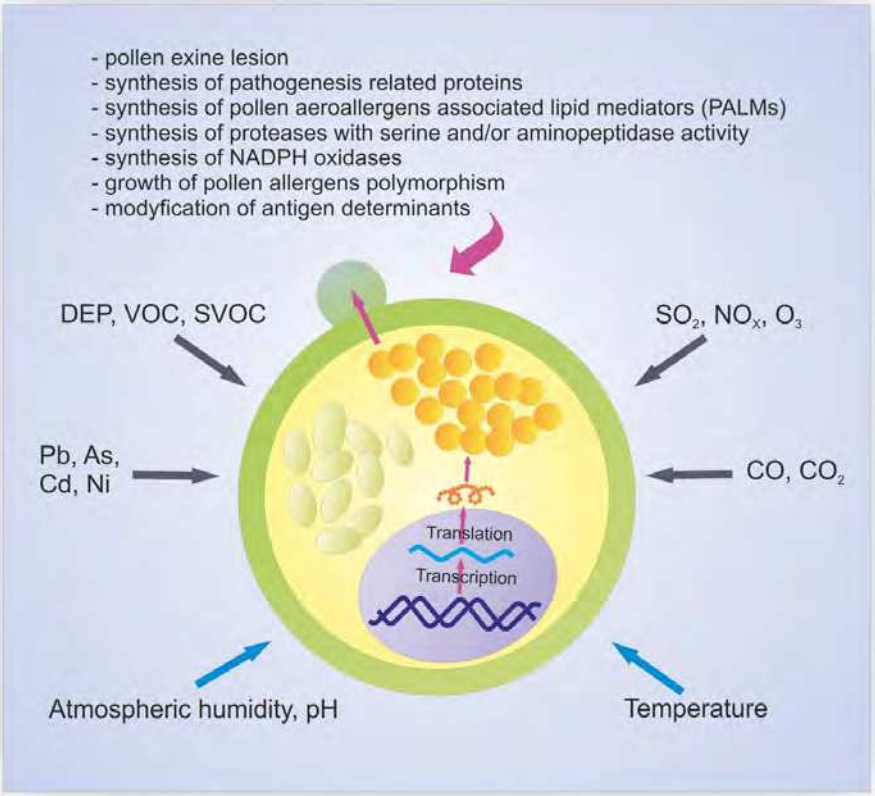


Fig. 3. Greater allergenicity of pollen allergens, collected from polluted areas, would be determined by chemical reactions between pollutants and pollen extracts and nonspecific modulation of synthesis machinery for many proteins, lipids and enzymes in response to environmental stress. Adopted from: Risse U, Tomczok J, Huss-Marp J, Darsow U, at al. Health- related interaction between airborne particulate matter and aeroallergens (pollen). Journal of Aerosol Sci. 2000;31, Suppl.:27-28.

phytoprostanes (lipophylic counterparts of prostaglandins) from pollen grains. The phytoprostanes are highly water soluble; they can get to the lower airways and inhibit the production of IL12 by dendritic cells, thus favouring Th2 response [31].

Many scientists point out the effect of pollution on climate warming, intense expansion of thermophilic plant species and readier exposure to their allergens, e.g. ambrosia allergens [152]. It is true that in some countries climatic warming lengthens the flowering season, contributes to the increase in the number of pollen grains, synthesis of modified proteins and allergenicity of some of the proteins. Strong winds resulting from weather anomalies transport pollens and their allergens. Together with toxins, which react with pollens and allergens, they cover long distances.

In their studies, Eckl-Dorna et al [38] showed that increased concentration of ozone contributes to the increase in the number of allergens of rye pollen from groups 1, 5, 6 as well as panallergens such as profilins. However, according to other studies, some air toxins can reduce the level of allergens. The exposure of grass pollen to an increased level of many toxins simultaneously, e.g. NO_2+O_3 or NO_2+SO_2 induced the decrease in levels of typical allergens; Phl p1b, Phl p4, Phl p5, Phl p6 and Phl p13, detected with an immunoblotting method and specific IgE antibodies of sensitized rats. The decrease in the levels of these allergens, according to the authors, might have resulted from mechanical or post-translational modifications of these proteins, under the influence of pollutants. It was difficult to detect them since the test highly sensitive and specific. There are plans to carry out further studies with the use of spectrometric methods which should make it easy to describe possible molecular changes in the epitopes of pollen allergens.

The existence of pollen grains in the atmosphere is based on the regular cycle of vegetation and flowering. The exposure to plant pollen fungal spores depends on many factors, among others, geographical latitude, global and local air circulation, weather factors, the level of urbanization of the environment and air pollutants. Numerous parameters characterizing climate warming, perceivable in many regions all over the world, influence the course of phenology and pollen distribution. Direct factors, such as temperature and precipitationas, well as more extreme weather phenomena, either induce the production of pollen or reduce it.

The indirect effects of higher temperature include the early blooming of trees, transport of pollen over a long distance and modification of flora (including the expansion of thermophilic taxons of plants such as ambrosia). In many centres which carry out long-term agrobiological and phenological studies, earlier and longer flowering seasons of allergenic plants have been observed. Biological observations performed by Ariano et al. [9] in Italy for 27 years showed a 25% increase in the level of pollen as well as an increase in the length of pollen seasons *Parietaria* (=85 days), olive (=18 days) and cypress (=18 days). It was shown that intensive exposure to pollen allergens contributed to the increase in the incidence of allergic episodes in people sensitized to pollen allergy in comparison to mite allergens. Kosisky et al [81] published the results of their twelve-year observations from Washington. They stated that although the level of pollens measured globally did not increase, the number of days with higher pollen counts did: by about 258% for grasses and by almost 12% for trees. Studies conducted in Switzerland over 21 years, gathered by Clot

[28] showed no particular changes in the pollen level. It should be pointed out that intensive production of pollen by plants can depend on many other factors, such as artificial fertilizers in the environment, an increase in the size of rural areas because of not cultivating arable land, development of soil erosion and desertification [112].

Apart from plant pollen levels, aeroallergens are also the subject of studies. Singer et al [123] showed a dangerous increase in allergen content in ambrosia pollen grains under the influence of increased concentrations of greenhouse gases. The response to the raised amount of CO_2 was a raised level of the most important allergen of that taxon, Amb a1, despite the fact the number of ambrosia pollen grains produced did not increase [21]. The results of a study performed in London showed the effect of allergen activity and air pollution ($<PM_{10}$) synergy can be spectacular; asthma was aggravated as a result of a 25% increase in IgE levels in the serum of patients sensitized to grass or tree pollen [50]. Air pollutants induce adjuvant effects which favour inflammatory processes, immunization and aggravation of asthma and allergy. Many studies highlight a positive relationship between the number of hospitalizations, high level of plant pollen and exceeding the maximum concentration of air chemical pollutants, especially SO_2 and PM particles.

2.10 Environmental pollution and pathogenesis-related proteins (PR)

It was confirmed that in unfavourable environmental conditions such as a pest invasion, the presence of microorganisms and fungal spores, exposure to fertilizers, air pollution caused by ozone, ultraviolet rays, phytohormones, pesticides, artificial fertilizers, the growth of temperature, plant cells synthesize pathogenesis-related proteins (PR), which are very often allergenic for humans. Interestingly, about 25% of the described plant allergens gathered in the database of International Union of Immunological Societies (IUIS), are (pathogenesis-related (PR) proteins. The mechanisms of their synthesis are still unknown. PR proteins, including, among others, isoflavone reductases and plant antibiotics, are numerous and usually belong to various families. The most common PR proteins have been classified into 17 families, marked PR1 – PR 17 according to taxonomic classification, molecular sequence, biochemical and functional characteristic as well as the response generated by the human immune system [137,138].

Many PR proteins have a high allergenic potential and great cross-reactivity. For example, PR-3 is a chitinase, the synthesis of which is an common reaction of plants to heavy metals, and the expression of Cup a 3, a PR-5 cypress allergen, is significantly higher in the pollen of plants grown in polluted areas [127]. PR proteins from group10 include ribonucleases and proteins similar to the main allergen of birch pollen: Bet v 1 and e.g. hazelnuts: Cor a 1 [124]. The enhanced synthesis of PR in plant cells and pollen contributes to a growing number of allergic reactions, including dangerous oral allergy syndrome (OAS) and even analyphylactic reactions. In sensitized patients suffering from pollen-food allergy syndrome, the first syndrome is allergy to inhalant allergens [19], especially in the city environment.

Interestingly, until recently, pollen grains have been considered simple, even primitive structures, dependent on vegetative organs of plants and inactive in a metabolic sense. However, thanks to the analysis of the pollen genome and the profile expression of particular genes, it has been possible to have a greater insight into the unusual transcriptional dynamics of pollen. It was concluded that while ripe pollen is relatively

resistant to air pollution in dry air, an increase in humidity triggers a cascade of reactions resulting in activation of highly dynamic metabolic processes, as well as a rapid increase in the process of gene transcription, synthesis of new compounds and conformational modifications of the existing proteins. A classification of transcripts carried out with bioinformatical analysis (DNA-ChipAnalyzer, GeneChip ® Array Genome) has made it possible to identify more than 51,000 compounds, many of which have been classified as PR proteins. In various stages of pollen life, i.e. starting with its creation, then development and germination of pollen tube, there are many changes in gene profiles and expression which take place and which depend on external factors and the toxins present [91]. It can be concluded that plant pollen should be treated as an aerobiological index for atmospheric pollution.

3. Allergens of fungal spores and pollution

Fungal spores are important elements of bioaerosols. Continual climate warming, demonstrated by an increase in temperature, precipitation and floods, causes increased exposure to fungal spores, both in the internal and external environment. Fungal spores have a many-faceted influence; they can induce mycosis, and the proteolytic enzymes and toxic products of metabolism known as called mycotoxins can damage epithelial protective barriers and have pro-inflammatory cancerogenous properties. β-glucans of fungal spores have adjuvant effects which indirectly favour the development of allergies by activating Th2 lymphocytes [67].

Exposure to fungal spores and plant pollen is measured by the volumetric method: measuring the number of spores per $1m^3$. Another method involves measuring the level of fungal products e.g. 1 – 3 β-glucans, which can demonstrate pro-inflammatory properties, both in atopic and non-atopic patients. According to Becker et al [12] the incidence of allergies to fungal spores (unlike to pollen allergens) can be underestimated due to lack of proper standardization of commercial extracts of some fungi such as Aspergillus or Penicillium. The spores of widely known fungi such as Cladosporium, Penicillium, Aspergillus, Helminthosporium and many other species are considered pollutants and infectious factors, as well as important risk factors for the development and aggravation of allergies and asthma. Studies carried out in the north of Poland indicated a minor influence of air pollution on the number of Alternaria and Cladosporium spores in $1m^3$ [51]. Some other studies have shown that pollutants can cause an increase in virulence of fungal spores. It has been confirmed that pollution induces the increase in the synthesis of melatonin in the conidia of Aspergillus fumigatus fungi, which leads to aggregation and makes them more resistant to lysis after being phagocitized by macrophages. The melatonin of mould spores can also contribute to the increase in virulence by not inhibiting apoptosis in macrophages which phagocitose the conidia of fungal spores. It also increases their resistance to ultraviolet rays [139].

Research on Aspergillus fumigatus showed demonstrated the possibility of activating a dozen or so mechanisms of cell signalling, mainly mitogen-activated protein kinase (MAPK). It was concluded that, like in plants, environmental factors activated the genes responsible for the synthesis of PR proteins, enzyme modification and synthesis of pigment which intensified the virulence of fungal spores, induced inflammatory processes and killed

experimental animals [1]. Studies carried out in polluted areas in Asia indicated that increases in air temperature, wind speed, rainfall and pollutants (e.g. solid particles – aerodynamic diameter ≤10 μm (PM10) and carbohydrates) increased the number of fungal spores in the atmosphere [24]. People who suffer from low resistance to fungal spores can develop serious infections such as Aspergillosis. It was stated that the exposure of the respiratory system to Aspergillus fumigatus spores can stimulate the production of IFN-γ by specific Th1 (CD4+) lymphocytes or Th2 (CD4+) cytokines, thus favouring allergies, depending on the phenotype of experimental animals [117,84].

The studies showed that the conidia of Cladosporium spp., Stachybotrys spp. and Aspergillus niger are considerably resistant to the activity of pollution, also with ozone [80]. Only high levels of ozone (which increase in cities when the temperature is >30 °C and humidity is low ≥40%) can inhibit the development of fungal spores e.g. Cladosporium spp [39,141].

3.1 Fungal spores can be considered serious air pollutants

It was concluded that the exposure to Aspergillus fumigatus and allergens of house-dust mites favours the development of asthma and the allergic inflammation of the respiratory tract. It thus enhances the activation of congenital and acquired immunological response. Fukahori et al. [47] showed that a strong reaction of dendritic cells to a simultaneous exposure to fungal spores and Der f1 might result from the activation of TLR2 receptors by the β-D glucan of the fungal spores, which in turn, leads to a synergetic activation of dendritic cells by mite allergens. Stimulation or blocking of TLR receptors as well as increases in IL-10 and IL-23 can change the balance of Th1/Th2/Th17/Treg and their influence on the course of allergic reactions. Recently Liu et al [93] presented the results of the exposure of Th2 lymphocytes in mice sensitized to Aspergillus fumigatus allergens and DEP particles. During in vitro studies they noticed epigenetic changes which involved hypermethylation of IL4 and IFNγ gene promoters, which led to polarization of Th lymphocytes toward Th2. Methylation of both the gene promoters was correlated with an increase in IgE level, which might imply that proteins of fungal spores, like air pollutants, can play a role in the pathogenesis of asthma and allergy through epigenetic mechanisms.

4. The environmental pollution and the oxidative stress

4.1 Pathways of toxin penetration.

Particles of dust and toxins are mostly absorbed by the lungs but also by the skin and alimentary tract and even by the placenta, which has a negative influence on a foetus.

4.2 Exposure to toxins of respiratory epithelium.

Human lungs constitute an area of 100 -140 m^2 , they are strongly vascularized and are constantly exposed to infectious factors and environmental pollution. Healthy lungs absorb air at the rate of 14 breaths per minute, which equals about 10 litres per minute and about 10,000 – 15,000 litres per day. Inhaled air, before it gets to the lowest located parts of lungs, is partly filtered and climatized. The mucous membrane in the nose prevents the largest polluted particles from getting inside the body. In order to cleanse themselves, lungs use

their cilia, which expel polluted mucosa at 16 beats per second. The respiratory epithelium is a protective barrier which actively protects the body and, if needed, activates the cells of the immunological system. Proteins such as filaggrin, loricrin and involucrin play an important role in reinforcing the epithelium against attack. They make it stronger and more resistant to invasion of microorganisms, allergens and chemical compounds. It was concluded that both epigenetic changes in genes caused by environmental pollution and cytokines of Th2 lymphocytes e.g. IL 4, IL13, TNF-α inhibit the production of filaggrin and other proteins, which might favour immunization, development of atopic dermatitis, allergy and asthma due to increased epithelial permeability [76,102]. In sensitive people, air pollutants, including allergens, can be bound by proteins and lipids of the epithelial cell membrane and thanks to them, can penetrate the inside of the cell.

Epithelial cells can initiate various protective initiatives against air pollution. One example might be the activation of numerous genes (300 – 550). The activation usually leads to the growth of the synthesis of pro-inflammatory cytokines and activation of cells which phagocytose many fractions of dust, allergens and bacteria [101,10]. Studies show that exposure to pollution induces cell stress. This, in turn, activates very complicated mechanisms adjusted to particular situations through increased expression of particular transcriptional factors, the synthesis of protein (e.g. SKN-1/Nrf) and the activity of proteasome in utilizing unneeded particles. These processes facilitate the maintenance of homeostasis of cells and protects them against activation of neoplastic processes and autoaggression [92].

In high levels of pollution and environmental toxins, these natural mechanisms are insufficient. It has been confirmed that the amount of PM particle fractions which penetrate the lungs depends not only on the size of the inhaled particles but also on the ability of the organism to cleanse and detoxify itself, which is genetically determined. However, in people who are exposed to nicotine smoke for a long time, neither detoxifying enzymes nor antioxidative protective mechanisms function properly, which favours bronchial hyperreactivity, asthma and lung-remodelling process.

Figure 4 shows the relative sizes of inhaled particle, patterns of their airway deposition and main health effects of air pollution.

4.3 The environmental pollution and the oxidative stress.

Each organism is constantly exposed to both endogenic and exogenic oxidizing compounds. Endogenous free radicals – reactive oxygen species (ROS), such as: O_2– , OH*, H_2O_2 and nitrogen - reactive nitrogen species (RNS), e.g. NO*, $ONOO^-$ are constant products of chemical reactions associated with respiration and processes within cells such as activated phagocytes and eosinophils active in allergic processes, and are considered the main source of ROS. In physiological conditions, free radicals pose no threat because of natural enzymatic and nonenzymatic protective systems of an anti-oxidative character [99]. Exogenous free radicals are neutralized mainly in the mitochondria of lung epithelial cells. The key antioxidant is glutathione. The synthesis of protective compounds in relation to ROS is stimulated among others by the activation of transcription factors, e.g. Nrf2, which leads to the activation of proteases and antioxidants and modulates inflammation by the inhibition of the NF-κB pathway. The activation of the Nrf2 metabolic pathway is important in the prevention of many inflammatory diseases, neurodegenerative diseases, diabetes,

pulmonary fibrosis and neoplasms, additionally, Nrf2 overexpression in neoplastic cells protects the cells against the cytotoxic activity of antineoplastic drugs [126]. The activation of Nrf2 might ameliorate the degree of lung impairment caused by nicotine smoke [130].

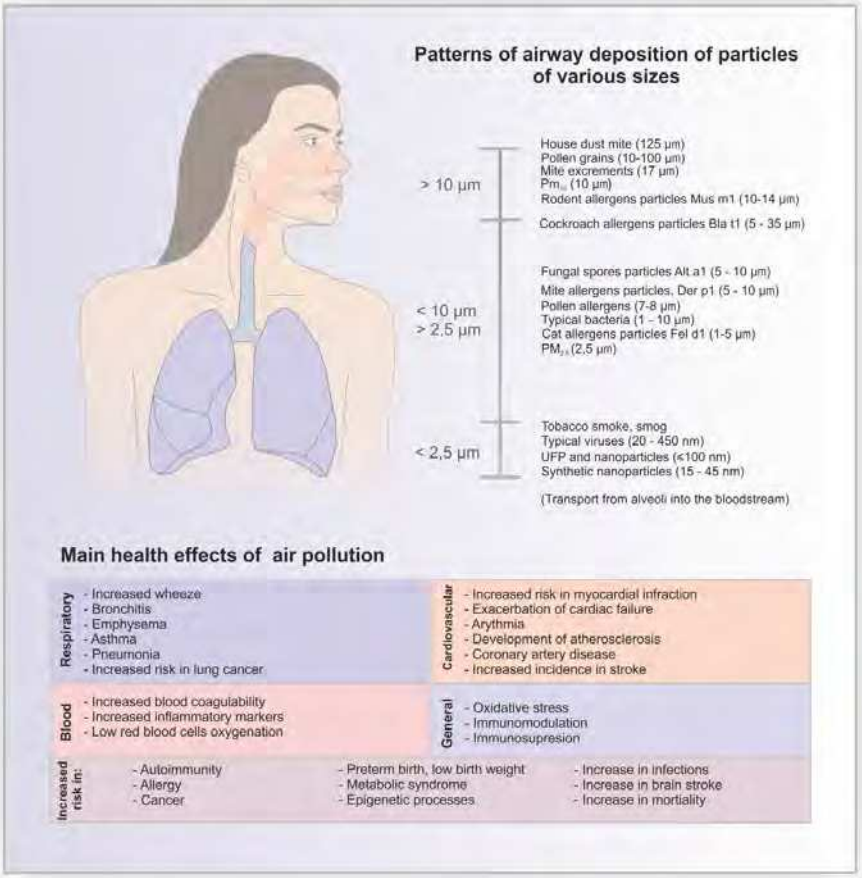


Fig. 4. Relative sizes of inhaled particle, patterns of their airway deposition and main health effects of air pollution. PM - particulate matter, UFP-ultrafine particles (particles <100 nm). Adopted from: Chang C. The immune effects of naturally occurring and synthetic nanoparticles. Journal of Autoimmunity. 2010;34:234-246.

4.4 The oxidative stress and the cascade of inflammatory effects induced by polluted air

The hierarchical model of oxidative stress presented in figure 2 shows the negative effects of the exposure to environmental pollution.

Level 0: Preventing the production of free radicals.

A lot of enzymes prevent the development of chain reactions leading to appearance of free radicals, e.g. glutathione peroxidase.

Level 1: Antioxidative cell protection.

The first stage of protection includes binding free radicals and breaking the cascade reaction. Here antioxidative enzymes and metalloproteins, i.e. proteins which bind ions containing copper and iron, are active. The second stage of protection includes ROS "scavengers": flavonoids, vitamin A, vitamin C, bilirubin, uric acid and glutathione. Relatively mild oxidative stress stimulates cell structures mainly through Nrf2 nuclear transcription factor for transmission signals for the expression of proper genes, production and activation of a numerous group of antioxidants.

Level 2: Inflammation.

If protective mechanisms turn out to be insufficient in neutralizing the excessive number of free radicals, it is difficult to maintain homeostasis. Moreover, an increase in the cascade expression of many pro-inflammatory genes for cytokines, chemokines, adhesive molecules and the heat-shock proteins active in inflammatory processes [71]. The activity of NF-κB transcription factor inhibits Nrf2, which decreases the expression and gene transcription of antioxidants essential in detoxification. The disturbance of the proper function of Nrf2 genes can also impair antigen presentation in the mechanisms of major histocompability complex class II, which makes the body more susceptible to both allergic and infectious diseases [144]. It has also been confirmed that the exposure of a mouse with $Nrf2^{-/-}$ to DEP particles, even to small doses , leads to an increase in bronchial hyperreactivity and oesinophilic inflammation of the respiratory system [87].

Level 3: Damage to mitochondria, cell apoptosis.

The third level of oxidative stress which is impossible to neutralize by protective mechanisms breaks the protective system. Great stress induces changes to Ca2+ ion concentrations, permeability of mitochondrial membrane and disturbances of mitochondrial functions. It contributes to energetic insufficiency of epithelial cells and the release of factors leading to apoptosis. Such processes are induced especially by PM particles and ultra small dust particles (UPF<0.1 μm) collected in urbanized city areas as they are characterized by a higher potential for ROS induction in cells than PM_{10} and $PM_{2,5}$ particles [88]. It is worth mentioning that apoptosis protects the body against the development of neoplasms, especially in the polluted environment.

4.5 Reactive oxygen species (ROS) and bronchial asthma

Excessive exposure to environmental pollution leads to the development of unnecessary ROS and RNS species. They attack cell membranes, disturb their electric potential and proper function of ion pumps. Oxidized cholesterol favours the development of atherosclerotic plaque. Overactive pro-oxidative processes might induce imbalances and induce the oxidizing process. The synergy of endogenous and exogenous anti-oxidants, which might neutralize free radicals, plays a key role in the protection against the development of inflammation of the respiratory passage and aggravation of asthma. The

activation of the Nrf2 pathway is to a great extent, proof of adaptation to the natural environment and factors. The anti-oxidative activity of Nrf2 is reduced in patients with severe asthma [104]. Children with severe asthma demonstrated posttranslational modifications of Nrf2 and impaired protection against free radicals. Thus, it was stated that ″redox status″ and the activity of Nrf2 can be invaluable in the assessment of asthma severity [43].

5. The role of aryl hydrocarbon receptor (AHR) in immunotoxicity

AhRs are considered the most important receptors in the detoxification and discharge of toxins and are represented by a few proteins, including Hsp90 (heat-shock proteins). They are present in the cell cytosol and naturally activated by bilirubin, arachidonic acid, eicosanoids such as prostaglandins, leukotriens, metabolites and some natural compounds present in food (tryptophan derivatives, diet carotenoids). It was discovered that AhRs are activated by over 400 exogenous compounds and that in turn, the activation of an AhR triggers the activation of cell transcription factors.

The TCDD dioxin is one of the strongest AhR ligands as it can securely bind these receptors. Unfortunately, toxins accumulate in the body and, as the half-life for dioxins is between 7 and 10 years, long-term AhR activation might be favoured with a consequential activation of genes encoding the enzymes metabolizing xenobiotics, which induces a chronic suppression of the immune system. Therefore TCDD is regarded as one of the most toxic and carcinogenic environmental toxins [56]. The receptors, having bound to ligands, move to the nucleus, where they activate gene expression , especially those responsible for the synthesis of enzymes involved in the metabolism of toxins, such as superoxide dismutase, glutathione peroxidase and aromatic hydrocarbons hydroxylase (from cytochrome P450 group).

Binding an AhR to a toxin leads first of all, to the development of toxic metabolites. Secondly, it induces changes to gene transcription. Researchers observed stimulation of the transcription of cytokine IL-17, which leads to the recruitment and differentiation of neutrophils, and IL-22, which is essential in the synthesis of defensins necessary in antibacterial immunity. An excess of IL-17 can disturb the balance of Th1/Th2 as well as the balance of Th17/Treg and, consequently, contribute to intensive development of inflammation, autoimmune and neoplastic diseases [150]. Exposure to TCDD increases risk of the development of granulocytic leukemia by up to 400%. The onset of the disease might happen even 15 years later [14]. An excessive amount of toxins might bind to DNA, RNA as well as cell proteins and induce a number of pathologies [54,68,143].

6. Dysfunctions of immune system in the polluted environment

Environmental pollution might cause immunomodulation and the immunosuppression of immune response [128], demonstrating insufficient anti-infectious and anticancer immunity [57]; they may also concern hypersensitivity, including allergy [15] or autoaggression [42]. Research findings indicate that even short-term exposure to toxins in the air can lead to an increase in the incidence of disease and death. It has been estimated that in Canada, air pollution contributed to about 8% of deaths in 2004 and as many as 10% in 2008 [3] The reaction to chemical agents present in the surroundings varies based on the individual.

Genetic factors, age, sex, physical condition, medicines taken, activity of endogenic detoxifying enzymes, past diseases and various factors connected with lifestyle, dietary habits and other risks, such a place of living, exposure to nicotine smoke: they all determine different reactions to environmental chemical agents. Allergy and atopic asthma are also effects of interactions between genetic susceptibility and the polluted environment, which has a great influence on the development of atopic phenotype, especially during rapid development in the prenatal and postnatal period [58]. Intensive exposure to allergens might have an impact on the development of tolerance. Yet, coexistence of toxins usually causes adjuvant activity. Early exposure to toxic substances, e.g. dioxins from nicotine smoke, PM particles, DEP, ozone might stimulate and preserve the Th2 atopic phenotype dominant in pregnancy. The process can be accompanied by suppression of Th1 cell proliferation. It might lead to the increased risk of the development of atopic asthma in children [96].

6.1 The examples of pollutants influence on the immunological response

6.1.1 Coal compounds

Coal destroys ecosystems and pollutes the environment when it is transported, stored and burnt. Also storing waste has negative implications on the environment. The process of burning coal is considered the main cause of global warming as it is responsible for the 30 % growth of CO_2 and methane (CH_4) in the atmosphere compared to the pre-industrial age [116]. Toxic substances in waste and ash (e.g. chromium, cadmium, mercury, arsenic) can contaminate potable water and food, and volatile fractions of ash can emit radiation 100,000 times stronger which nuclear power stations producing the same amount of energy**.**

Health status is the ability of the body to adapt to changeable surrounding conditions. However, stress induced by excessive exposure to exhaust fumes and environmental toxins is directly connected with the development of chronic inflammation of lower air passages and even leads to the increase in death rate. A memorable smog which happened in Belgium in 1930 [106] and in London in 1952, and a high level of SO_2, which lasted for 5 days in the smog, killed thousands of inhabitants of the city. At that time, the energy source was coal. In Silesia, Poland, where coal was mined on a relatively high scale in Europe, the mortality rate for young men (until 1989) was about 40% higher than the average national mortality rate . Also in Germany between 1995 and 1998, researchers observed a higher mortality rate which was closely connected with air pollution [111]. Sang et al. [121] confirmed that an increased risk of hospitalization and death resulting from SO_2 exposure might be connected with its influence on excessive activation of Cyclooxygenase-2 (COX-2) and prostaglandin PGE2, which leads, among other things, to the development of inflammatory state and even neurotoxic activity.

Carbon monoxide (CO) appears as the result of exhaust fume emission, fires and volcanic eruptions. If coal is burned properly, the emitted fumes contain about 1% CO. a safe level for a human. In the case of insufficient oxygenation, fumes can contain as much as 30% CO. The compound formed by binding hemoglobin and CO is called carboxyhaemoglobin, and the process not only occurs 200 times more readily than in the case of oxygen, but the product is more durable. A thirty-minute exposure to 0.1% – 0.2 % CO leads to death.

6.1.2 Nitrogen compounds

In the 20th century, the amount of nitrogen introduced to the cycle in the biosphere more than doubled and the process is still continuing. Nowadays, apart from pollutants characteristic of "the age of coal and steel" (mainly SO_2 and PM) many other products of burning crude oil and its derivatives used in industry, as well as road and air transport exist. They have been emitted for more than 200 years and their level is constantly increasing. The transport sector is the second greatest source of CO_2 emission in the EU; in the years 1990 – 2009, its emission increased by 20%. However, these fuels are not burnt completely and apart from CO_2, ever more toxic volatile and reactive nitrogen species (RNS) known as NOx, O_3, SVOC are being released into the atmosphere. It is estimated that transport is responsible for about 75% of the nitrogen oxide pollution . Apart from emitting pollutants, vehicles raise dust into the air , which might lead to greater bioavailability of allergens of plant pollen and fungal spores, as well as particles of latex from car tyres. As a result, there might be an increase in allergies to plant pollen, fungal spores as well as latex [116].

The natural level of nitrogen oxide ranges from 0.1 to 9.4 μg/m3. The WHO defines a 1-h limit value of 200μg NO_2/m3 air, equivalent to 0.1ppm NO_2. However, recent studies showed that thirty-minute exposure of nasal epithelial cells in tissue culture to 0.1ppm NO_2 resulted in cytotoxicity and genotoxicity [78]. NO_2 levels ranging from 100 ppb to 400 ppb may impair proper functioning of lungs and the level above 5ppm might lead to damage. [65] In many industrial cities, the NO_2 level is about 2 ppm [73]. It was concluded that NO_2 level in the air outside depends on population density and intensity of transport. [17]

Due to their poor water solubility, the site of toxicity of nitric oxides is the upper respiratory tract. Studies carried out on healthy volunteers demonstrated that a two-hour exposure to transport pollutants analyzed at an underground station in the centre of Stockholm (in peak hours) led to the increase in the expression of markers of Treg cells and activation of fibrinogen in the blood [119] Jeng et al [69] confirmed that a five-day constant exposure to PM_{10} particles resulted in an increase in fibrinogen level and IL6 level (i.e. cytokines which stimulate B-lymphocyte differentiation to plasma cells and synthesis of antibodies). But for people with asthma, even a short exposure to transport pollutants might turn out to be hazardous. Sixty patients with asthma were naturally exposed to city pollution for two hours by walking along Oxford Street in London. The studies on short-term exposure to city exhaust fumes demonstrated that, despite the lack of subjective symptoms, forced vital capacity (FVC) and one second forced expiratory volume (FEV_1) values were considerably reduced in comparison with the values gathered from the control group. Apart from those different values, an increase in marker level in sputum (such as mycloperoxidase marker - MPO) and a decrease in pH in respiratory passages were also observed [103].

6.1.3 Particulate matters (PM)

Particulate matters (PM) are emitted directly to the atmosphere (primary PM) or produced from gas precursors, e.g. SO_2, NO_x, NH_3, VOCs (secondary PM). PM is represented by solid and liquid particles which can be of organic or inorganic character. It can be inhaled and accumulated in the lungs. Exhaust fume emission, burning fuels, refining processes and other kinds of environmental contamination contribute to the production of PM, which is usually classified on the basis of particle size. The following fractions are monitored most

frequently: PM_{10} (< 10μm), $PM_{2.5}$ (<2.5 μm), $PM_{0.5}$ (<500nm), $PM_{0.1}$ (<100nm). PM_{10} are usually spherical, aerodynamic particles whose diameter is about 10μm. The toxicity of PM depends mostly on the chemical composition of the particles. Exceeded level of PM is considered an air quality index in EU countries. In cities, fractions of particles are mostly <2.5 μm, and over 80% of fractions have a diameter of <0.1 μm. The new trend, however, sounds optimistic; between 1990 and 2008 emission of PM particles decreased in European countries on average by 21%, but slight increase in the fractions of PM 2.5 – 10 μm was also observed [61]. Study findings carried out in Łódź in the centre of Poland in 2009 showed the maximum daily amount of PM_{10} being exceeded 35 times [64]. Research conducted in China and India indicates that the increase in PM_{10} level in city air by 10 $\mu g/m^3$ contributed to an increase in mortality rate by 0.6% [27].

$PM_{2.5}$ might induce some extra disorders in the cardiovascular system. Very small particles coming from exhaust fumes can enter the bloodstream and reach distant organs such as the heart and kidneys. There is also the possibility of micro-injuries of endothelial cells appearing in blood vessels which might affect the activation of coagulation factors and impair autonomic regulation of heart rate, which in turn, may cause sudden death because of arrhythmia [44].

The main cell lines involved in immunological response are epithelial cells, dendritic cells, Th lymphocytes, macrophages, neutrophils, mast cells, basophils and eosinophils. They protect the body's well-being but in a polluted environment, these cells can also get involved in the cascade of events leading to inflammation and various pathological forms. Many studies indicated that exposure to PM_{10} particles exacerbates symptoms in patients with asthma, contributes to increased administration of anti-asthmatic medications and frequent visits to emergency medical services [7]. Particles appearing in city and industrial areas are especially dangerous. Studies on air aerosol gathered in Bejing, with a population of twelve million , indicated that over 99% of PM particles had a diameter smaller than 1μm and the endotoxin level can reach a value of about 1250 pg/mg of aerosol. High immunomodulating, toxic and even mutagenic potential might be caused by the presence of many toxins and their easy deposition in lungs owing to very low weight [142]. It was concluded that they can inhibit the synthesis of IFNγ in human leukocytes of peripheral blood. As a result, the balance of the Th1/Th2 leukocyte population is disturbed. The dominant leukocytes are Th2 leukocytes which are responsible for the development of allergy. Simultaneously, anti-infectious and anti-neoplastic immunity gets reduced. Dockery et al [35] confirmed the relationship between $PM_{2.5}$ in the air and death rate. Cohort studies conducted in 6 cities in the US showed that $PM_{2.5}$ increase by about $10g/m^3$ in a year entailed an increase in death rate ranging from 10.9% to 20.8% [120]. Rezentiti et al [114] concluded that transferring children living in cities to unpolluted rural areas contributes to quick and considerable improvement of aspects of their health state such as well-being, peak expiratory flow (PEF) and monitored inflammation indicators (the decrease in the number of oesinophils in nasal lavage and the level of nitrogen oxide in exhaled air). Studies performed in Bejing indicate that extremely small particles stimulate pulmonary oesinophilia and the activation of Th2 response, which might be connected with the presence of β-glucan of fungal spores in inhaled urban particulate matter (UPM) [53].

6.1.4 Nanoparticles (ultrafine particles UFP)

Nanoparticles (ultrafine particles UFP). They belong to a class of the smallest PM particles: <100 nm. Two types of nanoparticles are recognised: natural nanoparticles emitted in the process of incomplete burning by diesel engines, and synthetic ones (produced deliberately) which have medical applications (e.g. in antibacterial nanocoating), electronic engineering and other industries. Many scientists stress their exceptional ability to penetrate the deepest parts of lungs and the inside of the cell. Research performed with the use of an electron microscope confirms that nanoparticles can damage even the internal structures of mitochondria [89]. They can easily get to the cardiovascular system and cause arrhythmia by changing cardiomyocyte contractility [145]. It was concluded that they can have some pro-inflammatory properties, raise blood pressure and favour atherosclerosis [8]. During exposure to UFP, mononuclear cells are chemotactically activated. The exposure also induces the expression of pro-inflammatory genes in macrophages and endothelial cells and stimulates the synthesis of pro-inflammatory cytokines, e.g. IL1B, TNF, IL4 [48]. The particles act through congenital and acquired immunity mechanisms and influence the development of Th2-type allergic inflammation of the upper respiratory tract [75]. As they are relatively large and light, they absorb many organic compounds, making them even more toxic. Li et al [90] stated that chemical composition of UFP, emitted by high-pressure diesel engines in trucks, was different for different working cycles of the engines. UFP particles emitted by stationary trucks directly induced oxidative stress in human aorta endothelial cells, and UFP particles emitted while the truck was moving contained four times more metal ions (iron, chromium and nickel) and more intensively activated inflammatory processes such as the increase in the gene expression for IL-8 chemokines and monocyte chemoattractant protein -1 (MCP-1) as well as adhesive molecules.

6.1.5 Diesel Exhaust Particles (DEP) – Toxin transporters

Diesel Exhaust Particles (DEP) – toxin transporters. Exhaust fumes which appear in the process of combustion of fuel oil tend to aggregate into separate, spherical particles which have a diameter of 0.1-0.5μm. The core of the DEPs are tiny specks of soot which are mixed in with hundreds of organic and inorganic substances. The influence of DEP particles on the immune system depends on the level of exposure, the particle diameter, their chemical composition, and their reactions with other chemical compounds, both organic and inorganic, including allergens and bacterial endotoxins. Experimental and epidemiological research shows that DEPs in city air have a more toxic action than those in a rural area. What's more, their effects can be reversible or irreversible, as manifested by various pathologies such as damage to epithelial cells, pulmonary emphysema, allergic asthma, cardiological disorders and even acute renal failure [107]. Studies have addressed the many mechanisms responsible for adverse immunological DEP-induced response and have demonstrated that that epithelial cells in the respiratory system are the first to detect pollutants and react to them, as DEPs can diffuse through the cell membrane and bind to receptors in the cytoplasm. One of such receptors is the aryl hydrocarbon receptor (AhR). Internalization of DEPs to the inside of the cells activates numerous signalling pathways which induce, inter alia, the synthesis of granulocyte-macrophage colony stimulating factor (GM-CSF) in the respiratory tract. This is essential in asthma pathogenesis as inducing the differentiation process of hematopoietic cells into precursors of granulocyte, macrophage and eosinophil lines favours proinflammatory changes in lungs. Having been exposed to

DEPs , the epithelium releases a number of mediators which have chemotactic properties and influence dendritic cells. These, in turn, activate naive T lymphocytes, which causes a proliferation of their clones in various effector lines. Of the examined air pollutants, DEPs from city areas are considered most allergenic [148]. A body of research shows that exposure of dendritic cells to PM particles stimulates Th to produce IL13 and IL1 and inhibits IFNγ. DEP extracts induce oxidative stress in bone marrow dendritic cells, which causes disturbances in the production of IL-12 cytokine, which plays a key role in the process of Th1 lymphocyte proliferation. Exposure in the early stage of life may be critical for the stability of the Th2 phenotype. As research demonstrates, DEP-induced oxidative stress contributes to the activation of Th lymphocytes, induction of Th2 cytokine and sIgE synthesis as well as the proliferation of eosinophils, release of inflammatory mediators, and goblet cell hyperplasia. Nasal administration of DEP solution performed in healthy non-smokers at a dose of 0.3 mg (daily corresponding dose in Los Angeles) induced an increase in IgE level in nasal lavage [34].

Many experiments have confirmed that DEPs modify the immunological response in relation to allergens and induce immunological reactions in the respiratory tract, even in response to low levels and short exposures [94]. They also stimulate increased expression of cell adhesion (ICAM1 and VICAM1), which might lead to thrombosis, acute ischemic stroke and an increase in cytokine levels, i.e. IL6 and IL10 as well as histamine and also the increase in the number of neutrophils and platelets [129]. In patients with asthma, DEP exposure leads to the development of metacholine-induced bronchial hyperreactivity. It was confirmed that DEPs can weaken antibacterial immune functions. In animal experiments DEPs proved to inhibit the expression of major histocompability complex class II molecules which are on antigen presenting cells and inhibit the ability of bacterial antigen presentation [32]. They also inhibit the activation of T lymphocytes and the T-dependent immune response to the dangerous zoogenous bacteria Listeria monocytogenes. They also modulate IL10 synthesis, which acts as an inhibitory factor for immune response. In such conditions, bacteria living in phagocytes can easily proliferate [149].

6.1.6 Policyclic aromatic hydrocarbons (PAHs)

Policyclic aromatic hydrocarbons (PAHs) are benzene derivatives such as xylene, toluene, pyrene and benzpyrene. They penetrate cell membranes, accumulate in the lipids of various tissues, mainly in the liver and bone marrow. According to research , cigarette smoke is an important source of PAHs. PAH metabolites were traced in pregnant women living in city areas in Canada [108]. They had strong immunosuppressive properties which, in experimental animals, were represented by pancytopaenia, inhibition of cell immunity and also humoral, i.e. IgA, IgE deficiency, in response to thymus-dependent and thymus-independent antigens, deficiency of proteins of the complement system as well as the impairment of phagocytosis connected with blocking Fc receptors. Moreover, it was confirmed that PAHs influence human B lymphocytes and stimulate the effects of class switching of antibodies, which enhances IgE synthesis [132]. Metabolites of these compounds are also hazardous as they are characterized by genotoxic properties [1,49].

6.1.7 Dioxins

Dioxins – a general name of more than 200 chemical compounds from the group of chlorinated hydrocarbons. They are built of two benzene rings connected with two oxygen

bridges. They are produced in the burning process of plastic products, the production of herbicides and disinfectants and while smoking cigarettes. In the air and soil they are not diluted with rainwater but they accumulate in the body in lipids. They are known as "the most toxic chemical compounds ever produced by man". For example, dioxin TCDD – tetrachlorodibenzodioxin is known for its strong carcinogenic properties. Experiments on animals showed that dioxins demonstrate immunotoxic properties. The effects of TCDD exposure merit research as these compounds, even in low concentrations, demonstrate a wide spectrum of activities and are hence known as "environmental hormones". Dioxins have been proven to decrease the expression of major histocompability complex class II and exposure to larger doses causes atrophy and suppression of the thymus – a place where T lymphocytes mature [134]. When adsorbed,dioxins on PM particles reach the lungs they are phagocytized by pneumocytes – epithelial cells of the respiratory system. From there they are transported by blood to the liver where they bind to an AhR receptor. The exposure of animals even to minimal doses of TCDD (0.01lg/kg of body weight) caused a stable binding of the compound to the AhR receptor, which inhibited the proliferation of bone marrow stem cells and activated the immunosuppression [13]. They can also bind to estrogen receptor (ER), which might disturb the activity of estrogens and other hormones, and also induces degradation of ER receptors [52]. These toxins, depending on the size of the dose, have an impact on $CD4^+$ lymphocytes and stimulate their differentiation to T-helper as well as Th1, Th2 and Th17 effector lymphocytes. They also promote the development of suppressive Treg lymphocytes.

Although cell proliferation is considered an irreversible process, it has recently been discovered that dioxins such as TCDD can inhibit the differentiation of B cells into plasmatic cells by changing the expression of transcription factors. Large doses of these dioxins can contribute to the change in programming completely differentiated plasmatic cells back to B lymphocytes. The effects of the change in programming mature B lymphocytes to the cells which have progenitor phenotype [16]. It was stated that they might disturb proper functioning of steroids. They also play a role in the modulation and synthesis of many important cytokines, e. g. TNFα, IL1, IL6, TGFα, TGFβ and IL4 and the exposure to dioxins in a pre-natal period induces hazardous immunosuppression [85,131,23]. Dioxins were proved to disregulate the expression of many genes, among others, in epithelial cells of the respiratory passage, which contributes to the occurrence of many genotoxic symptoms, such as production of unusual proteins, including ubiquitins, and these in turn, disturb transcription processes, favour autoimmunization and the development of neoplasms in fetuses of experimental animals [55,70,140].

6.1.8 Ozone (O_3)

Ozone (O_3) - is a form of oxygen with three atoms in a molecule. The ozone layer which spreads at the height 10 – 50 km from the ground positively contributes to thermal balance of the Earth and absorbs 99% of UV radiation, which has fateful implications for all living organisms, although the same wavelength is responsible for vitamin D production. O_3, unlike other toxins, is a secondary pollutant, since it is produced from the hydrocarbons and nitrogen oxides of which air is composed with the use of natural sunlight. The half-life for tropospheric ozone is around 22 days [63]. Ozone is a strong oxidizing, irritating and

bactericidal agent. The reaction of ozone with water molecules leads to its hydrolysis and the production of free radicals. Reactions of O_3 with air pollutants change the chemical composition of smog. They enhance its irritating properties for the eyes, mucous membrane of the respiratory passage.

Being a strong oxidant, ozone can react with many biomolecules inside and outside a cell. It disturbs the metabolism and photosynthesis of plants. It has a negative influence on the respiratory and alimentary systems and also on the skin. It was stated that ozone might have caused more than 20, 000 premature deaths and about 200 million episodes of respiratory failure within only one year [136]. Many authors also stress that O_3 and symptoms of allergy, asthma and chronic obstructive pulmonary disease (COPD) are closely related [33,46,77]. The early exposure to ozone might favour the Th2 atopic phenotype, which leads to a more probable risk of the development of allergy and asthma in children. Kopp et al [79] conducted studies in which they monitored allergy symptoms in 170 children. They concluded that the symptoms were aggravated as the ozone level rose, however, after some time, the symptoms became more stable despite the ozone level remaining relatively high. The researchers showed that frequent inhalations with 0.5 ppm of ozone and house dust mite (HDM) carried out for six months in young atopic monkeys induced the amplification of immune response , the increase in IgE levels, oesinophilia, changes in the respiratory tract, an increase in bronchial hyperreactivity and histamine level in serum. Inhalations performed exclusively with ozone lead to the increase in histamine level in serum, probably on the IgE-independent way [122]. According to Peden et al [109] ozone induces pro-inflammatory effects with accompanying mechanisms not examined well yet (in comparison to other air pollutants) in which monocytes and macrophages take part. Ozone was also confirmed to increase P substances in the respiratory tract [82].

7. Epigenetic changes and environmental pollution

Epigenetic modifications are considered a bridge connecting the genotype and phenotype of living organisms. Air pollutants can contribute to many epigenetic changes, by changes to gene expression, e.g. by DNA methylation and changes to histone structure. They also might facilitate the transcription activation of promoters and modification of RNA segments or make these processes difficult to occur. The dynamics of epigenetic modifications are varied [6]. It is believed that some genes may become activated only if they are affected by environmental exposure, for example to nicotine smoke, as well as by PAHs which induce chromosome aberrations and oncogenic mutations. [110]. It can be concluded that epigenetic changes induced by the polluted environment play a key role in the development of asthma and allergic diseases. They can modify transcription of genes connected with immune reactions, induce pro-inflammatory response and simultaneously cause remission or aggravation of the disease and even control the effectiveness of pharmacological treatment [11,83]. These changes are usually reversible but they can also be hereditary. Research is being performed on epigenetic biomarkers essential in the early stage of life and their role in the development of asthma and allergy in later life, as well as the relationship between the findings of clinical observations made during exposure to pollutants and gene expression for many important factors, e.g. Treg cells.

8. Conclusions

A polluted atmosphere is only one of many examples of destruction of the natural environment. There is sizeable body of evidence confirming the considerable anthropogenic influence that exists on air composition and even the climate on the Earth. These human activities influence all forms of life, including the life of man himself. Our immune system stays alert and strives to minimize the risk of exposure to hazardous level of air pollutants which might posses synergistic and antagonistic properties. The degree of sensitivity to air pollutants is different for each individual. It depends on age, health condition and genetic factors. It is therefore difficult to determine the maximum levels of environmental toxins. We are ever more aware of the source of the problems of environmental pollution. Nevertheless, it is difficult to solve them. Reasonable pro-health education seems to contribute considerably to the improvement of air quality and the condition of the natural environment. The mentioned problems should be solved on a world scale.

9. Acknowledgments

We thank Dorota Wawrzyniak for translation of manuscript and Agnieszka Wojciechowska for all pictures. We are also grateful for the time and efforts of Edward Lowczowski in reviewing this manuscript.

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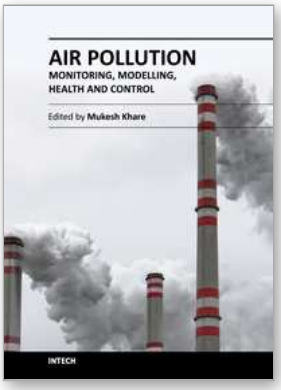

Air Pollution - Monitoring, Modelling, Health and Control
Edited by Dr. Mukesh Khare

ISBN 978-953-51-0381-3
Hard cover, 254 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

Air pollution has always been a trans-boundary environmental problem and a matter of global concern for past many years. High concentrations of air pollutants due to numerous anthropogenic activities influence the air quality. There are many books on this subject, but the one in front of you will probably help in filling the gaps existing in the area of air quality monitoring, modelling, exposure, health and control, and can be of great help to graduate students professionals and researchers. The book is divided in two volumes dealing with various monitoring techniques of air pollutants, their predictions and control. It also contains case studies describing the exposure and health implications of air pollutants on living biota in different countries across the globe.

How to reference
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Barbara Majkowska-Wojciechowska and Marek L. Kowalski (2012). Allergens, Air Pollutants and Immune System Function in the Era of Global Warming, Air Pollution - Monitoring, Modelling, Health and Control, Dr. Mukesh Khare (Ed.), ISBN: 978-953-51-0381-3, InTech, Available from: http://www.intechopen.com/books/air-pollution-monitoring-modelling-health-and-control/allergens-air-pollutants-and-immune-system-function-in-the-era-of-global-warming-

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