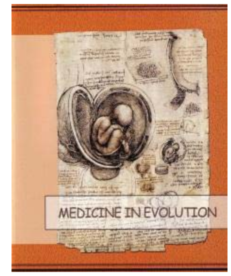
Review
Is air pollution involved in the epidemiological manifestation of viral infections with respiratory tropism?



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Abstract

The article is a synthesis of current information from the literature regarding the link between chemical atmospheric pollutants and their impact on respiratory tract infections. The viruses most frequently involved in respiratory pathology are represented by: respiratory syncytial virus, adenoviruses, influenza virus, parainfluenza, rhino - and enteroviruses, after the SARS epidemic, MERS and COVID-19 pandemic, coronaviruses are etiological factors with significant fatality. The most common air pollutants are: PM10, PM2.5, NO, NO_2, SO_2, and soil level O_3. Increased levels of these pollutants influence the incidence and fatality of viral respiratory infections. Unlike PM10, which remains confined to the upper respiratory tract, PM2.5 penetrates deep into the respiratory tree, causing local inflammatory reactions and impaired defense mechanisms. Also, the increase in susceptibility to respiratory infections is correlated with long-term exposure to high concentrations of: NO, NO_2, SO_2 and O_3.

Keywords: atmospheric pollution, COVID-19, respiratory infection

INTRODUCTION

Air, the main component of the atmosphere, the gaseous shell that surrounds the Earth, is made of nitrogen (79.2%), oxygen (20.8%) and in an insignificant proportion, carbon dioxide, ammonia and water vapor. [1] It is considered a polluting factor, any substance in the air in excess, which could cause environmental disturbance, human discomfort and health disorders. Physical, chemical and biological pollution are known. The main air pollutants are: nitrogen oxides (nitrogen monoxide NO and nitrogen dioxide NO_2), suspended particles (as main representatives PM10, PM2.5), sulfur dioxide (SO_2) and ground-level ozone. (O_3).

SUSPENSED PARTICLES - represents a complex mixture of solid and liquid particles, of various sizes, the most important being PM 10 (with a diameter between 2.5 and 10 µg / m^3), respectively PM 2.5 (with a diameter less than 2.5 /µg / m^3). These particles come from natural sources (volcanic eruptions, rock erosion, soil particle suspension, sandstorms, aerosolization of pollen or sea waves) or from anthropogenic sources (road traffic, both by burning fossil fuels and by friction produced at the level of tires, agricultural and industrial activity - especially in the chemical and extractive fields, waste treatment). Larger diameter particles tend to remain in the nasal mucosa, while smaller ones slightly exceed this filter and reach the respiratory shaft, causing changes in respiratory cilia motility, inflammatory reactions and exacerbation of chronic lung pathology. In order to prevent harmful effects on human health and / or the environment, reference intervals are established, with internationally accepted values. Thus, according to law no. 104/2011, in force in Romania, the daily limit value for PM 10 is 50 µg / m^3, the annual limit value 40 µg / m^3, while the limit value established as a target until January 1, 2020, is 20 µg / m^3 . For PM 2.5, the annual limit value is 25 µg / m^3 and the limit value set as a target until January 1, 2020, is 20 µg / m^3. [1, 2, 3, 4, 5]

OZONE is a stifling smell gas, very reactive, and oxidizing. If at atmospheric level 15-40 Km above earth's shell, offers protection against UV, ground level ozone represents a pollution factor. It is produced by chemical reactions between the sun's rays and organic gases, nitrogen oxides, emissions from power plants, refineries, chemical plants or road traffic. It has an irritating effect on the nasopharyngeal mucosa, produces pulmonary pathological changes even after the disappearance of acute symptoms, so it is considered to be a risk factor for asthma and a worsening factor for chronic lung disease. According to the Romanian legislation, the threshold alert is 240 µg / m^3 for a period of 3h consecutive, the information threshold at 180 µg / m^3, for a period of 1h, and the target value is considered 120 µg / m^3. [1, 2, 3, 4, 5]

NITROGEN OXIDES - The main nitrogen oxide present in the air is represented by nitrogen dioxide (NO2), with a toxicity 4 times higher versus nitrogen monoxide (NO). The main source comes from the burning of fossil fuels, from industrial activity, from electricity production or from engine emissions. They are responsible for the formation of smog, reduced visibility in urban areas, the greenhouse effect and the appearance of acid rain. Increases the incidence of chronic respiratory pathology (asthma, chronic bronchitis), increases the number of hospitalizations and the death rate from lung pathology. The limit values for NO_2 are set at 200 µg / m^3 for the hourly limit, 40 µg / m^3 for the annual limit and 30 µg / m^3 - the critical level for vegetation protection. The alert threshold value was set at 400 µg / m^3, measured for 3 consecutive hours, at representative points, on an area of at least 100 km^2 or for an entire area. [1, 2, 3, 4, 5]

SULFUR DIOXIDE - is a colorless gas, with a pungent, bitter, non-flammable odor, water soluble, resulting from the burning of sulfur. It comes from natural sources - phytoplankton, bacterial fermentation in swampy areas, volcanic eruptions by oxidation of sulfur-containing gases, but also from burning fossil fuels in electrical installations, the activity of oil refineries, cement factories or materials processing industry. Short-term exposure to high concentrations of sulfur dioxide causes severe respiratory distress, and long-term exposure predisposes to respiratory tract infections. It especially affects extreme ages and aggravates pre-existing lung diseases. It also potentiates the harmful effects of ozone. The hourly limit value for the protection of human health is set at 350 µg / m^3, the daily limit value at 125 µg / m^3 and the critical level for the protection of vegetation at 20 µg / m^3. The alert threshold, of 500 µg / m^3, is determined by measuring for 3 consecutive hours in representative points, on an area of at least 100 km^2 or on an entire area. [1,2,4,5]

Aim and objectives

This article aims to synthesize the knowledge from the specialized literature regarding the link between atmospheric chemical pollutants and their impact on acute viral respiratory infections.

Acute respiratory tract infections are a major cause of morbidity and mortality today, among all age groups and in all geographical regions. Pneumonia, one of the lower respiratory tract infections, affects 450 million people annually, with 3 million deaths worldwide in 2016, 2.56 million deaths in 2017, making it the 4th leading cause of death in world and the pathology transmissible with the highest fatality (for 2016). [6,7] Its incidence is 5 times higher in developing countries versus developed ones and from an etiological point of view, viral pneumonia occupies a main place , with approximately 200 million cases annually.

The relationship between air pollution and respiratory pathology was investigated before the current pandemic of COVID 19, in an attempt to quantify the correlation between pollution and morbidity / mortality from respiratory infections.

Since 2003**, Cui.Y. et** al studied the relationship between Air Pollution Index (API) - derived from CO, NO_2, O_3, PM, SO_2 concentrations and fatality from SARS, highlighting that the population in areas with moderately high Air Pollution Index has a risk of death from SARS with 84 % higher versus those living in regions with low API [RR = 1.84; 95% CI: 1.41-2.40], and the population in areas with high API has a double risk of mortality from SARS versus those living in areas with low API (RR = 2.18; 95% CI: 1.31 -3.65). [9]

In a study conducted in 6 cities in Italy, in the period 2001-2005**, Faustini. A et al**. demonstrated that a 10 µg/m^3 increase in PM 10 values leads to an increase in hospitalizations for respiratory diseases by 0.59% [90% CI: 0.10-1.08%] and outpatient mortality by 3.95% [90% CI: 1.53-6.43%], while a 10 µg/m^3 increase in NO_2 values determined an increase of 1.19% [90% CI: 0.23-2.15 %] of hospitalization following respiratory pathology. [10] Similarly, in a 2016 study by **Carugo. M et al**, in the Lombardy region, Italy, known for its high degree of pollution, showed that an increase of 10 µg / m^3 in PM 10 and NO_2 values corresponds to an additional mortality of 1.64% [90% CI: 0.56 -2.72] for PM 10 and 0.46%, respectively [IC 90%: - 1.23-2.18] for NO_2. [11]

Reilly.P.J in 2018 also identifies a correlation between elevated levels of air pollutants and acute respiratory distress syndrome (ARDS), when exposure to air pollutants occurs over a longer period of time. [12]

In a study conducted between 2010-2017 on a cohort of 19,093 patients at the Hospital in Antwerp, the province with the highest concentrations of PM 2.5 in Belgium, **Annik De Weerdt et al** reported an association between the duration of artificial ventilation and exposure to air pollutants, 10 days before admission. [13]

After the previous flu pandemic, a study conducted in Asia in 2010 by the team led by **P.S. Chen** identified higher concentrations of the 2009 AH_1N_1 virus in the air during sandstorms, when concentrations of air pollutants - PM2.5, PM10 and CO, were higher than on clear days. [14]

Wei Su and colleagues reported in 2019 in Jinan, China, a correlation between increased concentrations of air pollutants (PM2.5, PM10, SO_2, CO) and increased risk of developing influenza-like illness (ILI). Thus, a 10 µg/m^3 increase in PM 2.5 concentration was associated with an increase in the relative risk of developing ILI of 1.01 [95% CI: 1.01-1.02], for an increase of 10 μg/m^3 of PM 10 concentration, RR increased by 1.001 [95% CI: 1.00-1.01] and for a similar increase in SO_2 concentration, increased by 1.00 [95% CI: 1,0003-1.0012]. The increase in O_3 values was negatively correlated with ILI [RR 0.99; 95% CI: 0.98-0.99]. [15] Also, in 21 cities in China, in the period 2013-2014, the 10 PM μg / m3 increase in PM2.5 was associated with an increase of 1,010 [95% CI: 1,003-1,018] per day and 1,006 [95% CI: 1,000.11.012] at three days, of the number of cases of measles, determined by a morbilivirus also transmitted by air. [16]

The positive correlation with the high concentrations of PM10, PM2.5, NO_2, NO, respectively the negative correlation with O_3 were also relevant in the study of **Wang.L et al,** from 2019. [17] In the same year, **C. Liu et al** , analyzed the degree of air pollution and mortality recorded in 652 cities in various regions, predominantly in the northern hemisphere. A significant, positive association was observed between PM10 and PM2.5 concentrations and overall mortality. An increase of 10 μg / m3 of the PM10 / PM2.5 concentration was correlated with an increase of 0.47% [95% CI: 0.35-0.58], respectively of 0.74% [95% CI: 0.53-0.95] of daily mortality attributable to respiratory pathology. [18]

Another category of studies focuses on the etiopathogenic mechanisms through which air pollutants can intervene in respiratory pathology**. Wei Su et al** show that the presence of suspended particles facilitates and increases the ability of the virus to attach to respiratory epithelial cells, and to penetrate deep into the respiratory tree. It also decreases the ability of macrophages to phagocytose the virus, increasing the susceptibility to infection. [15]

In an experimental study**, Jeong.S** and his team inoculated intratracheally with the pollutant factor PM 2.5 to a group of mice, and found a significant increase in the number of macrophages and neutrophils in lung tissue at 24 hours after exposure. Persistence of leukocyte infiltrate in the lungs and liver has persisted for at least two days after exposure. [19] Jie Yang et al report a significant increase in IL4, TGF-β1 and TNF-α (tissue and serological levels), an increased number of inflammatory cells, intracellular edema and significant tissue damage in a group of mice exposed to high concentrations of air pollutants (PM2.5, CO, NOx) versus the control group in the laboratory. [20]

In a recent mini-review, from 2020**, Cao Y et al** describes the harmful effects of pollutants on hair epithelial cells, changes in their structure, which leads to reduced mucociliary clearance, a factor determined in the occurrence of respiratory pathology. It also reports the correlation between prolonged exposure to high concentrations of NO_2 and increased susceptibility to respiratory infections, with the risk of developing permanent lung damage. [2]

The emergence of the new SARS-COV2 coronavirus had as its starting point the city of Wuhan, Hubei Province, China, from where it spread very quickly around the world, with the onset of the COVID-19 pandemic in 2020. The speed of spread, the existence of seemingly random outbreaks, raised the issue of identifying the factors that led to this evolution, as well as the role of air pollution. Multiple recent studies have shown that pollution influences the transmission of SARS-COV2 coronavirus, but also sensitizes the respiratory tree by acting on protective mechanisms. The investigation of the pollution level of the regions with the highest number of cases, respectively the involvement of geographical factors were discussed especially in the Asian and Italian articles, in an attempt to identify the factors that led to the fulminant evolution of COVID 19.

Z.Yongjian et al (China, 2020) identify a positive correlation between the increase of O_3, CO, NO_2, PM10 / PM2.5 concentrations and the number of COVID-19 cases, simultaneously with a negative correlation between the number of cases and the SO_2 concentration, possible due to the virulicidal effect of SO_2. Thus, for a 10 μg / m^3 increase in PM2.5 values, an increase of 2.24% [95% CI: 1.02-3.46] was reported in the number of confirmed daily cases, for PM10 an increase of 1.76% [95% CI: 0.89-2.63], for O_3 4.76% [95%

CI: 1.99-7.52], and for NO_2 6.94% [95% CI: 2.38-11 51]. Instead, an increase in SO_2 values by 10 μg / m^3 determined a decrease in the number of daily illnesses by 7.79% [95% CI: -14.57-1.01]. [21]

Xiao Wu Ms et al (USA, 2020) investigating 98% of the population of 3000 counties, reports that an increase of 1 μg / m^3 in the long-term mean concentration of PM2.5 is associated with an increase in the mortality rate through COVID-19 with 15% [95% Cl: 5-25]. [22]

Travaglio. M et al (UK, 2020) in a study on the correlation of NO_2 and NO concentrations with the fatality rate of SARS COV2 cases, identified a correlation between increased NO_2 and NO concentration and the severity of disease forms in England, as well as a inversely proportional relationship between O_3 concentration and severity of COVID-19 forms, respectively with the number of deaths. [2. 3]

Conticini. E et al (Italy, 2020), in a study that hypothesizes that exposure to high concentrations of polluted air for a longer period, leads to a weakening of the defenses respiratory mechanisms, reports a correlation on the value of Air Quality Index (which measures the degree of pollution) and the number of deaths through Covid-19, in the regions of Lombardy and Emilia Romagna. After the onset of the pandemic, there was a decrease in pollution levels, but the number of cases did not decrease in direct proportion to them, which shows that the effects of pollution on the respiratory system are long-lasting and cannot be reversed in the short term. [24]

Fattorini. D et al (Italy, 2020) evaluated the distribution of air pollutants (PM2.5, PM10, NO_2, O_3) for 4 years and highlighted the high level of pollution in northern Italy, as well as the correlation between the degree of pollution and the number of cases of COVID-19 in 71 provinces in Italy. [25].

Ogen Y et al (Italy, 2020) highlighted two European areas that showed significantly increased concentrations of NO_2 between January and February 2020: northern Italy and the region of Madrid, Spain. Also these 2 regions presented the highest number of cases: Lombardy 2168 cases, Emilia Romagna 531 cases, Piedmont 175 cases, Veneto 115 cases, Madrid 498 cases, at the date of the study. Fatality was 12% for the regions of Lombardy and Emilia Romagna, compared to 4.5% in the rest of Italy. By March 2020, a total of 4443 deaths were caused by SARS COV2 in these two countries, and a percentage of 83% (3701 cases) of these deaths were recorded in areas where the NO_2 concentration exceeded 100 μmol / m2 . Both regions are surrounded by mountain ranges, and low airflows cause a concentration of NO_2 close to the earth's surface. Topographic conditions together with atmospheric ones prevent the dispersion of air and pollutants, which can cause respiratory diseases. [26]

Setti.L et al (Italy, 2020) after an analysis of 34 PM10 samples taken from the industrial region of the province of Bergamo, showed that the viral RNA of SARS-COV2 may exist associated with PM10 in the external environment, and in conditions of atmospheric stability and high concentrations of PM10, can lead to the appearance of clusters. [27]

CONCLUSIONS

In the current pandemic context, it becomes imperative to identify any risk factor and try to annihilate it, in order to control and subsequently stop this exacerbated manifestation of the epidemiological process. The most common air pollutants are PM10, PM 2.5, NO, NO_2, SO_2, and soil level O_3. Increasing the values of these pollutants, even by a few units, has a decisive influence on the incidence and fatality of viral respiratory infections.

Suspended particles with a large diameter, PM 10, remain largely confined to the nose and throat, while particles with a smaller diameter of PM 2.5 penetrate deep into the respiratory tract, affect mucociliary clearance, allowing agents to penetrate. deep tracheobronchial infections and increases the ability of the virus to attach. It also causes local inflammatory reactions, with a decrease in the body's natural protection capacity against inhaled infectious agents. The presence of NO and NO_2, SO_2, O_3 in high concentrations and long-term exposure are correlated with increased susceptibility to respiratory infections.

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