Advances on the immunotoxicity of outdoor particulate matter: A focus on physical and chemical properties and respiratory defence mechanisms

E. Nozza, S. Valentini, G. Melzi, R. Vecchi, E. Corsini

PII: S0048-9697(21)01459-5

DOI: https://doi.org/10.1016/j.scitotenv.2021.146391

Reference: STOTEN 146391

To appear in: *Science of the Total Environment*

Received date: 10 December 2020

Revised date: 16 February 2021

Accepted date: 7 March 2021

Please cite this article as: E. Nozza, S. Valentini, G. Melzi, et al., Advances on the immunotoxicity of outdoor particulate matter: A focus on physical and chemical properties and respiratory defence mechanisms, *Science of the Total Environment* (2021), https://doi.org/10.1016/j.scitotenv.2021.146391

Advances on the immunotoxicity of outdoor particulate matter: A focus on physical and chemical properties and respiratory defence mechanisms

E. Nozza[1,2], S. Valentini[2], G. Melzi[3], R. Vecchi[2,*], E. Corsini[1]

[1]Department of Environmental Science and Policy, Università degli Studi di Milano, via Balzaretti 9, 20133 Milan (Italy)

[2]Department of Physics, Università degli Studi di Milano, via Celoria 16, 20133 Milan (Italy)

[3]Department of Pharmacological and Biomolecular Sciences (DiSFeB), Università degli Studi di Milano, via Balzaretti 9, 20133 Milan (Italy)

*corresponding author: Prof. Roberta Vecchi, roberta.vecchi@unimi.it

Keywords

Particulate matter, respiratory infections, immunotoxicity, BioPM

Abstract

Particulate matter (PM) is acknowledged to have multiple detrimental effects on human health.

In this review, we report literature results on the possible link between outdoor PM and health outcomes with a focus on pulmonary infections and the mechanisms responsible for observed negative effects. PM physical and chemical properties, such as size and chemical composition, as well as major emission sources are described for a more comprehensive view about the role played by atmospheric PM in the observed adverse health effects; to this aim, major processes leading to the deposition of PM in the respiratory tract and how this can pave the way to the onset of pathologies are also presented. From the literature works here reviewed, two ways in which PM can threaten human health promoting respiratory infectious diseases are mostly taken into account. The first pathway is related to an enhanced susceptibility and here we will also report on molecular mechanisms in the lung immune system responsible for the augmented

susceptibility to pathogens, such as the damage of mechanical defensive barriers, the alteration of the innate immune response, and the generation of oxidative stress. The second one deals with the relationship between infectious agents and PM; here we recall that viruses and bacteria (BioPM) are themselves part of atmospheric PM and are collected during sampling together particles of different origin; so, data should be analysed with caution in order to avoid any false cause-effect relation. To face these issues a multidisciplinary approach is mandatory as also evident from the ongoing research about the mechanisms hypothesized for the SARS-CoV-2 airborne spreading, which is still controversial and claims for further investigation. Therefore, we preferred not to include papers dealing with SARS-CoV-2.

Introduction

Air pollution was ranked as the seventh highest risk factor for human health (Lim et al., 2012), being responsible for almost 3 million deaths per year globally. Among atmospheric pollutants, particulate matter (PM) represents a major challenge. Typically, due to its complexity as for e.g. size, chemical composition, sources, and chemical transformation in the atmosphere, and even if PM mass alone is a very poor metric to account for observed adverse biological and health effects (Cassee et al., 2013) it is still largely used to represent the “effective dose”

It is noteworthy that when PM samples are collected – typically on filters - atmospheric particles with very different origin are sampled all together; therefore, it is not possible to ascertain if a BioPM (consisting of a virus or bacteria) was natively a single particle in the air or was attached to a pre-existing particle; this is often a point which is not properly taken into account, leading to misinterpretation of the results pointing at a cause-effect relationship, which cannot be robustly proved. Other important points still poorly known (Groulx et al., 2018) are about the possible influence of aerosol particles of different origin on micro-organism, enhancing or inhibiting their viability in atmosphere and the probability of interaction between BioPM and other atmospheric particles (Belosi et al., 2021). In recent times, it has become clear that is

mandatory to use an interdisciplinary approach to investigate the relationship between particulate matter and biological effects, in order to face such complexity.

The first part of this review is aimed at recalling PM properties and sources in outdoor air; indeed, these parameters are sometimes under-considered in papers dealing with PM effects on human health. The second part of this work reports literature results concerning outdoor PM pollution and its correlation with respiratory diseases, mainly focusing on infectious ones. Of course, these are noteworthy also due to recent outbreak of the novel coronavirus SARS-CoV-2, that raised the attention of the world scientific community to better understand e.g. how the virus spread in air, what is its lifetime in different environmental conditions, which is the effect of ambient conditions on its viability, and what is the minimum dose for a possible transmission. However, the mechanisms driving airborne transmission of the SARS-CoV-2 is still quite controversial and further studies are needed although there are evidences that the probability of transmission in outdoor air due to respiratory aerosol (see e.g. Belosi et al., 2021 and references therein) is rather low while it is relevant indoor (Buonanno et al., 2020 and therein cited literature); for these reasons, the authors consider premature to focus on this hot-topic for a review paper and will mainly refer to literature published in the pre-COVID era.

In this review, results from a collection of works were selected with the methodology described below. The authors collected the bibliographic material for the present work from different databases (Scopus, PubMed, and Google Scholar) and following references reported in the retrieved manuscripts, in the period between April 2020 and January 2021. The papers, books, and other material cited were all available in English. Keywords used were “particulate matter”, “PM”, “air pollution”, “aerosol”, “bioaerosol”, together with “viral infection”, “virus”, “health effects”, “deposition”, “inhalation”: for each search, keywords were combined using the conjunction “AND”. Among all the results, the authors selected and cited 152 works; criteria used for this choice were: collection of papers focusing only on outdoor pollution and laboratory studies, collection of peer-reviewed works only.

1. PM: An heterogeneous ensemble with a variety of sources

Particulate matter (PM) – in the following referred also to as atmospheric aerosol - is characterised by physical-chemical properties (e.g. size, shape, composition, interaction with light) and mass/number concentration that can vary widely in space and time, making this mixture a highly heterogeneous ensemble. PM has detrimental effects on human health (Dockery et al., 1993; WHO, 2016) and has been also inserted in Group 1 of the IARC carcinogenic agents (IARC, 2016). Moreover, PM can affect Earth radiation balance, clouds, visibility, and air quality (Boucher, 2015; Fuzzi et al., 2015; Pöschl, 2005; Raes et al., 2002; Ramachandran, 2018; Seinfeld and Pandis, 2006; Tomasi et al., 2017).

PM properties depend strongly on sources types and formation pathways determining the particle size, that spans from a few nanometers to hundreds of micrometers (Seinfeld and Pandis, 2006). Major PM constituents are inorganic ions, such as NO_3^-, SO_4^{2-}, NH_4^+, organic and elemental/black carbon, mineral dust, and sea salt (Fuzzi et al., 2015; Monks et al., 2009; Ramachandran, 2018). Other minor constituents such as heavy metals can be found in PM in small concentrations, but they deserve particular attention as they can threaten human health (e.g. Tomasi et al., 2017 and references therein).

The contribution of different components to total PM mass varies depending on the site, the season, and the meteorological conditions. For instance, Putaud et al. (2010) have studied 60 locations in Europe, including urban, rural, and kerbside sites. The authors highlighted the relevance of NO_3^- and SO_4^{2-} at rural sites, compared to PM collected in urban areas; moreover, elemental carbon contribution to PM_{10} was observed to increase when moving from rural to urban to kerbside sites, whereas organic matter importance was similar at all locations; natural PM components as sea salt and mineral dust represented a relevant fraction of PM only at coastal sites and in Southern Europe, respectively (Putaud et al., 2010). Conversely, higher levels of ammonium sulfate, organic matter, ammonium nitrate, and in particular elemental carbon were detected by Hand et al. (2012) in US urban locations than in rural ones.

Moreover, PM composition is also strongly related to the size fraction; indeed, PM of natural origin comprises aerosols with diameters in the 2.5 – 10 μm size range (coarse particles e.g. resuspended dust, sea spray, and biological particles such as pollen, spores, plant debris) and anthropogenic particles are mainly originated by combustion processes and are characterized by smaller diameters (fine particles,

typically less than 2.5 µm in size). Aerosol toxicology data very often refer to laboratory studies using particles generated by combustion processes using fossil and/or biomass fuels (e.g. Devouassoux et al., 2002; Naeher et al., 2007) and thus observing effects due to a specific PM type which is far from the atmospheric one which has a high degree of complexity. Indeed, particle directly emitted in the atmosphere by combustion processes (i.e. fresh aerosols of primary origin) account only for a minor fraction of PM mass, which is largely explained by inorganic and organic aerosols produced in the atmosphere by gaseous precursors through gas-to-particle conversion (i.e. secondary aerosols) (Seinfeld and Pandis, 2006; Tomasi et al., 2017).

In the atmosphere, transport-related PM is produced by vehicular traffic (both exhaust emissions of particles and gaseous precursors and non-exhaust emissions), railroads, aircrafts, and ships. Composition of vehicle exhaust particles (generally smaller than 100 nm) is dominated by carbon (in particular from diesel vehicles), hydrocarbons, and NO_x (i.e. NO and NO_2, precursors of secondary aerosol); traffic non-exhaust emissions derive from abrasion of road pavement and wear of tyres, brakes, and mechanical components; Mo, Fe, Cu, and Sb (from brakes), Ba and Zn (from tyres)), Al, Si, Ca, Ti, and Fe (from dust resuspended by vehicles) are typical tracers found in particles with diameter larger than 2.5 µm (Pant & Harrison, 2013; and references therein). Awareness about traffic-related pollution adverse health effects and increased mortality risk promoted many studies on exhaust emissions in the last decades (see e.g. HEI, 2010; WHO, 2005; and references therein), opposite, non-exhaust emissions are still scarcely studied, although transition metals emitted have a high potential of inducing negative health effects e.g. through oxidative stress in biological tissues, inflammation responses and/or other toxic effects (e.g. Denier van der Gon et al., 2013).

Industrial activities are also a relevant source of several compounds which can cause health effects such as lung inflammation and damage causing respiratory chronic diseases (Riffault et al., 2015); the amount and composition of industrial PM varies according to the type of industry, the production process, the technology, and the materials used (e.g. Riffault et al., 2015; and references therein). For instance, sulfur,

heavy metals, and hydrocarbons are emitted by chemical, petrochemical, and paper industries, while iron and steel industries emit mainly C, Fe, Si, Ca, Mg, Pb, Zn, F, and metal oxides.

Combustion of fossil fuels and biomass (especially wood) for domestic heating can account for a large portion of carbonaceous PM in urban areas; physical and chemical properties of these particles depend on the fuel burned, combustion conditions, and appliances used (e.g. Amato et al., 2016; Calvo et al., 2013; Piazzalunga et al., 2011). Combustion processes generally produce PM with heterogeneous chemical composition (e.g. Chen et al., 2017; and therein cited literature) and tiny sizes (often with diameter smaller than few hundreds of nm), especially when the combustion is more efficient and takes place at higher temperature (Reid et al., 2005). Coal and oil emissions are dominated by C, S, and V; biomass burning emissions are mainly particles composed by C, Zn, K, Cl, and levoglucosan (e.g. Bhattarai et al., 2019; Reid et al., 2005). Many literature studies evidenced toxicological effects associated to combustion-related particles (e.g. Corsini et al., 2013; Donaldson et al., 2005), nevertheless atmospheric aerosol has several components, all of which can potentially cause health endpoints.

In addition to anthropogenic sources, PM can have a natural origin. One of the largest components of primary natural PM is marine aerosol (Calvo et al., 2013; Fuzzi et al., 2015). Sea spray can contribute to the increase in airborne bacteria concentration at coastal sites (Després et al., 2012; and therein cited literature). Another major PM component is mineral dust (MD). It is mainly natural, even though anthropogenic emissions (soil dust resuspended by human activities) were estimated to account for 25% of total mineral dust concentration (Ginoux et al., 2012). Recent literature studies (e.g. Després et al., 2012; Fröhlich-Nowoisky et al., 2016; Querol et al., 2019; Soleimani et al., 2020) have reported that desert dust outbreaks can have health impacts, being associated to the transport of biological particles (e.g. fungi, spores, bacteria, and viruses) and to high PM concentration episodes with daily PM_{10} concentrations up to 1000 $\mu g/m^3$ close to the emission source and 400-600 $\mu g/m^3$ at receptor sites (Querol et al., 2019).

Among biological PM components, bioaerosol (or BioPM, as will be referred to in the following), i.e. particulate matter of biological origin, is raising increasing interest related to its effects on human health

and climate. Major components of BioPM are bacteria and archaea, fungal spores and fragments, pollen, viruses, algae and cyanobacteria, biological soil crust (i.e. organisms living on the soil surface), lichens, and others (e.g. plant or animal debris) (Després et al., 2012; Fröhlich-Nowoisky et al., 2016; Healy and Sodeau, 2012; Hinds, 1999; Jones and Harrison, 2004; Kim et al., 2018; Nazaroff, 2016). BioPM size covers a wide range comprising particles with diameter from hundreds of nm to 10-100 μm. In terms of particle size, pollen is the largest (17-58 μm), followed by fungal cells and spores (1-30 μm), bacteria (0.25-8 μm), and viruses (<0.3 μm), while animal and plant fragments range in various sizes (Jones and Harrison, 2004). Their percentage distribution is not size proportional as the vast majority of BioPM, approximately 80%, is composed of bacteria. Up to 28% of total continental PM concentration can be constituted by BioPM (Jaenicke, 2005; Matthias-Maser et al., 2000; Matthias-Maser and Jaenicke, 1995) and it is estimated that its emission factor can be comparable to those of mineral dust and sea salt, i.e. about 1000 Tg/year (Jaenicke, 2005). Also animals and humans are important sources of BioPM, as they can constitute a primary source of some viruses, bacteria and fungi. In addition, areas impacted by human activities are characterized by higher BioPM concentrations (e.g. Nazaroff, 2016; and references therein). After emission, BioPM can be transported by wind similarly to dust, inside water droplets and ice crystals; it can undergo chemical reactions that can modify the molecular composition and biological activity of BioPM particles themselves; it is removed by gravitational settling and dry deposition or washed out by precipitations. Average residence time of BioPM was estimated to vary from less than 1 day to a few weeks (Després et al., 2012; and references therein), depending on particle physical-chemical properties.

2. PM and human health

After the infamous high pollution event occurred in London in 1952, the scientific community focused its interest in the study of air pollutants and their relationship with human health (Drinker, 1953). Since then, many epidemiological studies have reported the onset of pathologies and the increase of mortality after the exposure to pollutants, and especially to PM (WHO, 2016).

It is worth reminding that the occupational health community often classifies PM into inhalable, thoracic, and respirable size fractions according to its entrance into various compartments of the human respiratory tract (e.g. Brown et al., 2013; Hofmann, 2011; Ruzer & Harley, 2012; US EPA, 2004). The 50% penetration aerodynamic diameters for thoracic and respirable fractions are 10 µm and 4 µm, respectively (e.g. US EPA, 2004; Wilson et al., 2002). According to European air quality standards (Directive 2008/50/EC), the regulated aerosol size fractions are PM_{10} and $PM_{2.5}$, i.e. particles with aerodynamic diameter smaller than 10 and 2.5 µm, respectively; this size cuts were chosen following considerations on health and source apportionment studies (US EPA, 2004; Whitby, 1978; Wilson et al., 2002). PM_{10} can be considered an indicator of thoracic particles (US EPA, 2004; Wilson et al., 2002); $PM_{2.5}$ meets the need to separate fine and coarse particles and identify different sources of fine PM and is consistent with health effects investigated by epidemiological studies (e.g Brown et al., 2013; Dockery et al., 1993; U.S. EPA, 2019; and therein cited literature).

To safeguard the global population against the negative outcomes caused by high concentrations of particulate matter, WHO has established annual and daily threshold mean values for PM_{10} (20 and 50 µg/m^3, respectively) and $PM_{2.5}$ (10 and 25 µg/m^3, respectively) (WHO, 2016). Nevertheless, there are no evidence of a minimum concentration that guarantees a safe exposure (Shaughnessy et al., 2015); in fact, detrimental effects for human health were observed even at the exposure to 3 µg/m^3 $PM_{2.5}$ (Xia and Yao, 2019).

The effects of PM inhalation on humans can be serious, causing severe illnesses and death, and worsen pre-existing pathological conditions, after either acute or chronic exposures. In high pollution conditions the mortality rate is enhanced, and WHO attributed to PM 4.2 million deaths worldwide in 2016 (Ahmed et al., 2020). The adverse effects following exposure to PM range from irritation, coughing, headaches and vomiting (Carinanos et al., 2007), to the degeneration into pulmonary-related illnesses, such as reduced lung function, increased risk of infections (Ghio, 2014), development of chronic obstructive pulmonary disease (COPD), autoimmune diseases, and cancer (Peixoto et al., 2017; C. N. Zhao et al., 2019). Furthermore, the cardiovascular system can suffer from ischemia and myocardial infarction (Nemmar et al.,

2004), the nervous system can be affected by neurodegeneration and neuronal apoptosis, and even reproduction can be impaired by premature birth and prenatal death (Peixoto et al., 2017).

Among all the detrimental effects deriving from PM exposure, from now on, the authors will focus only on the ones linked to infectious diseases.

3. PM: A pulmonary threat

3.1 PM deposition in the respiratory tract

PM harmfulness depends on its penetration inside the respiratory tract (Deng et al., 2019; Zwozdziak et al., 2016a). Several factors can influence PM deposition in human lungs and the resulting health effects (Bui et al., 2020; Hofmann, 2011; Majid and Madl, 2011; Ruzer and Harley, 2012; U.S. EPA, 2019): biological factors, such as lung morphology and physiology (Bui et al., 2020; Hofmann, 2011; Majid and Madl, 2011; Ruzer and Harley, 2012; U.S. EPA, 2019); physical factors, including fluid dynamics of the inhaled air volume (Bui et al., 2020; Hofmann, 2011; Ruzer and Harley, 2012); particle properties (size, density, chemical composition, shape, electrical charge), and deposition mechanisms (Bui et al., 2020; Hofmann, 2011; Majid and Madl, 2011; Ruzer and Harley, 2012; U.S. EPA, 2019).

The breathing pattern is among the most important physiological factors affecting particle deposition in lungs. It is defined by the breathing frequency (i.e. number of breaths per minute) and the tidal volume (volume of air inhaled during a single breath). Also, the mode of respiration (nasal or oral) plays a key role in PM deposition, since the nose is far more efficient than mouth in retaining and removing particles. Furthermore, temperature and relative humidity can affect PM deposition as they vary depending on the mode of respiration and location inside the lungs (Ching and Kajino, 2018; Ruzer and Harley, 2012).

Breathability and clearance are two important parameters that determine the residence time and local distribution of PM in the respiratory tract, and thus its potential to cause damage. Breathability, i.e. the fraction of particles suspended in the air that enters nose and mouth during inspiration, primarily depends on particle size, breathing conditions, and wind speed (ICRP, 1994; Ruzer and Harley, 2012; U.S. EPA, 2019).

On the other hand, clearance refers to particles removal from the respiratory tract (ICRP, 1994). Major clearance mechanisms (Majid and Madl, 2011; Ruzer and Harley, 2012; U.S. EPA, 2019) are mechanical clearance, mucociliary (fast phase) clearance, macrophage-mediated (slow phase) clearance, particles translocation, and blood absorption. Their relative efficiency depends on particle properties (especially size, shape, and solubility) and varies in the different lung regions.

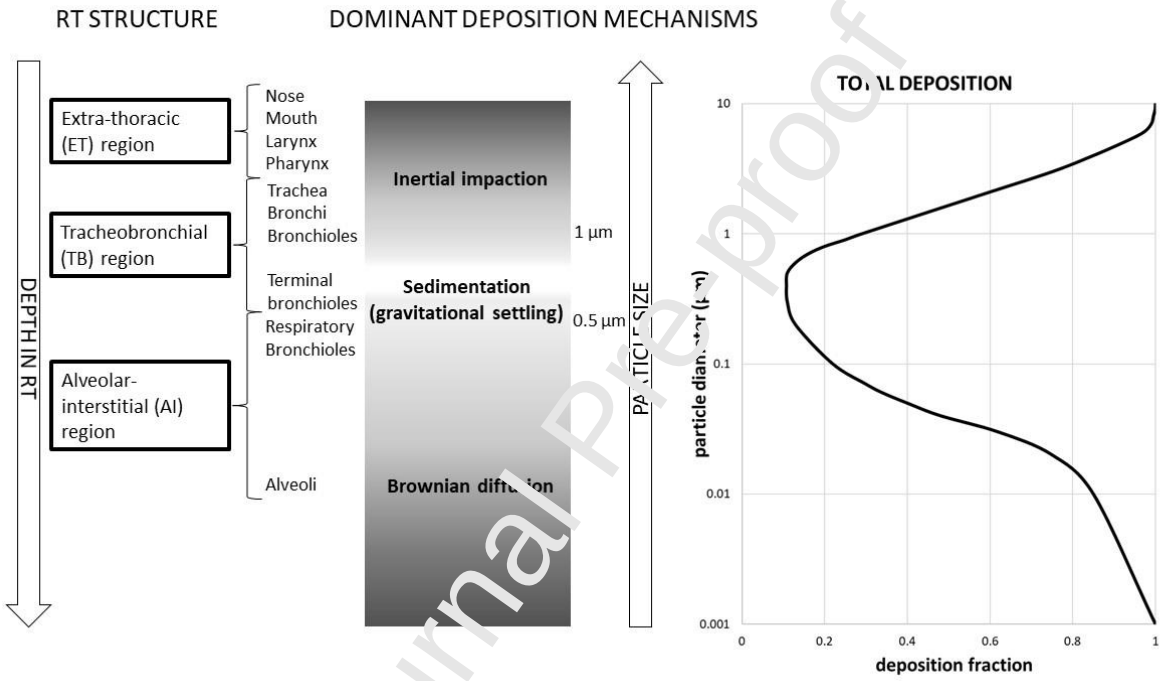


Figure 1 *Scheme representing the structure of human respiratory tract (RT), major deposition mechanisms acting in different RT regions and how their efficiency depends on PM size (colour coding: white=low efficiency; dark grey=high efficiency); the right part represents the typical pattern of total PM deposition in the RT as a function of particle diameter (based on* Hofmann, 2011*).*

PM deposition occurs through various mechanisms such as impaction due to inertia, sedimentation (gravitational settling), Brownian diffusion, interception, electrostatic precipitation, and convection (Hinds, 1999); the former three are the major processes involved in the deposition of inhaled particles in the respiratory tract (Bui et al., 2020; Hofmann, 2011; Ruzer and Harley, 2012; U.S. EPA, 2019; Madl and Majid,

2011), as also reported in Figure 1. In addition, interception has a role in the deposition of fibrous particles and chain-like aggregates (Hofmann, 2011).

As represented in Figure 1, the relative importance of these mechanisms varies with particle size (Hofmann, 2011; Seinfeld and Pandis, 2006; U.S. EPA, 2019). Total deposition fraction as a function of particle diameter has a minimum at 300-400 nm; lower diameters (below 100 nm) are dominated by diffusion, while efficient impaction and sedimentation characterize larger particles (above 1 μm). In addition, the shape of the curve describing PM deposition as a function of particle size exhibits a different shape in each region of the lungs, depending on the structure and geometry of the regions themselves and breathing pattern. PM deposition can be forecast using different models, suitable also for predicting local to whole-lung health outcomes (Hofmann, 2011). The most used are empirical or semi-empirical, deterministic, trumpet, and stochastic models (e.g. ICRP, 1994; Majid and Madl, 2011; Ruzer and Harley, 2012), even though also Computational Fluid Dynamics (CFD) and Artificial Neural Network techiques are being recently used (Bui et al., 2020).

Finally, also other factors can affect PM deposition in human respiratory tract, as they impact on lung geometry and ventilation (Brown et al., 2013; Bui et al., 2020; Majid and Madl, 2011; Ruzer and Harley, 2012): these include pre-existing diseases (e.g. COPD, asthma, cystic fibrosis) (Hofmann, 2011; Ruzer and Harley, 2012), age, gender and physical activity (Brown et al., 2013; Bui et al., 2020; Hofmann, 2011; Majid and Madl, 2011; Ruzer and Harley, 2012).

According to the size, coarse particles are inhalable and normally are deposited in the upper part of the respiratory tract (Figure 1) (Deng et al., 2019; Ghio, 2014). Despite the presence of mucus, cilia and other barriers, a fraction of fine particles (i.e. $PM_{2.5}$) can penetrate the lungs, where almost its half remains and penetrates into the tissues (Zwozdziak et al., 2016b). It is noteworthy that ultrafine particles can reach the alveoli and diffuse into the cardiovascular system by crossing the air-blood barrier (Rothen-Rutishauser et al., 2008; Upadhyay et al., 2014). In few hours, ultrafine particles (UFPs) can reach the main systems of the body, thus extending their negative action to the whole organism (Rothen-Rutishauser et al., 2007). Using a

rat model, Kreyling et al. (2009) demonstrated that in 24 hours, nanoparticles and their aggregates (size below 80 nm) can be collected in secondary organs as heart, brain, liver, skeleton, spleen, and kidneys and showed also an accumulation in the foetus.

3.2 Adverse health effects

PM action in the respiratory tract is generally pro-inflammatory, with increased production and secretion of signalling molecules as cytokines, chemokines, and adhesion molecules (Schwarze et al., 2006). The inflammatory condition can be prolonged by continuous recall of inflammatory cells, with production alongside of cytokines of other active compounds, as reactive oxygen species (ROS) and proteases (Peixoto et al., 2017; Schwarze et al., 2006).

The first pathological outcomes are irritation, decrease in lung function, and exacerbation of pre-existing pathologies as asthma, pneumonia or bronchitis. Subsequently, chronic effects may occur, which are characterized by a reduction in the expiratory flow and permanent remodelling of the lung tissue (Liang et al., 2014; Upadhyay et al., 2014; Van Eeden et al., 2005). In addition, PM exposure can lead to DNA damage, possible onset of mutation, and cancer (Corsini et al., 2013; Gualtieri et al., 2011; Marabini et al., 2017; Oh et al., 2011; Peixoto et al., 2017). Toxicological studies, mainly using human *in vitro* models, have determined that the most toxic PM components are metals (e.g. Fe, Cr or Cd), polycyclic aromatic hydrocarbons (PAHs), black carbon (BC), and other organic compounds. These substances can induce DNA detriment and micronuclei formation on different cells of the respiratory system, as well as trigger inflammation (Michael et al., 2013; Oh et al., 2011)

Another effect associated with the exposure to environmental pollutants - including PM - makes the picture more complex: this is a decrease of immune defences against pathogens, due to the alteration of a correct immunological response, which leads to an increased susceptibility to infections (Mishra et al., 2020; Zelikoff et al., 2003). Not only PM can result in immunotoxicity, but allergens and pathogens can be part of the biological component of PM (BioPM) (e.g. Menetrez et al., 2009).

Therefore, to investigate the possible detrimental effects caused by exposure to PM and its contribution to the onset and spread of infections, it is important to focus on two aspects: the immunosuppressive effects of PM and the role of BioPM as a source of infectious agents.

4. Immunotoxicity of PM

As mentioned above, the exposure to air pollution can increase the susceptibility to infections and worsen the conditions in those who are already infected (Ciencewicki et al., 2008). Increase in PM_{10} and $PM_{2.5}$ concentrations have been associated with the rise in the spread of bacterial and viral infections (Clifford et al., 2015a; Croft et al., 2019). The respiratory system is the first to be affected, but also severe systemic infections, as meningitis, have been associated to PM increases in the air (Ghio, 2014).

Among the factors that can influence the relationship between PM and infections, PM composition and meteorological conditions have to be mentioned. It has been shown that wood and biomass smoke, diesel engine exhaust, and generally PM containing high quantities of black carbon, have a detrimental action on the lungs, causing stress, and inflammatory condition (Grahame et al., 2014). This compromises subsequent macrophage activation, and also resulted in defective natural killer (NK) cells activity, leading to an increase susceptibility to infectious diseases (Castranova et al., 2001; Grahame et al., 2014). In addition, Clifford et al. (2015), in their laboratory study using geogenic PM (i.e. mineral dust), demonstrated a positive correlation between the presence of Fe ions and the deficit in lung anti-viral responses in a mouse model of influenza. This study has shown that geogenic PM_{10} exposure increases inflammation, impairs lung function and increases viral load, exacerbating the response to respiratory viral infection with iron being a driver of these responses.

Concerning the meteorological conditions and increased risk of infection, there are different opinions in the scientific community, with some papers demonstrating that influenza spreads more in winter months, but it was also reported that only in warmer winters with high relative humidity a better spread of viruses was observed (Jaakkola et al., 2014; Mirsaeidi et al., 2016; Van Noort et al., 2012). It is also worth recalling that ambient PM concentrations are driven by both emission/formation rates and dilution conditions in the

atmosphere; indeed, high pollution episodes often occur during winter periods as domestic heating is an additional PM source and atmospheric mixing layer is shallow as observed in well-known hot-spot pollution areas such as the Po Valley, in Northern Italy (Vecchi et al., 2007). Similar seasonal patterns with increasing PM concentration during the cold months, driven by atmospheric stability and strong emissions from fossil fuels combustion and agricultural biomass burning practices are reported in other heavily polluted areas such as China and India (see e.g. Gao and Ji 2018; Jain et al. 2020). Moreover, it is noteworthy that not only PM concentration, but also $PM_{2.5}$-to-PM_{10} concentration ratio and PM chemical composition show different behaviour depending on the location, the season, weather conditions, and activity of emission sources, with potentially varying effect on human health (Bell et al., 2007; Huegin et al., 2005; Yeh et al., 2017).

The increased susceptibility to infections due to PM is particularly relevant for viral infections. Acute respiratory infections are grouped in acute upper respiratory infections (AURI) and acute lower respiratory infections (ALRI). The former comprise cold, rhinosinusitis, and laryngitis while the latter include bronchitis, bronchiolitis, influenza, and pneumonia (Horne et al., 2018; Silverman et al., 2017). ALRI are due to both bacteria and viruses, with virus being the dominant cause. Among the viruses inducing ALRI, respiratory syncytial virus (RSV), influenza, parainfluenza, rhinovirus, and human metapneumovirus are some of the most common (Horne et al., 2018). Horne et al. (2018) demonstrated that the number of patients needing cures for ALRI increased to 15-32% following the rise of PM levels, and estimated that also the severity of infections can depend on the concentration of PM. In addition, Xia and Yao (2019) found a strong correlation between the increase of 10 $\mu g/m^3$ in $PM_{2.5}$ and the increase in hospital admission for ALRI of children (4.3%), and for AURI of both children and adults. Shaughnessy et al. (2015), focusing on a subgroup of young healthy adults between 18 and 39 years of age, estimated a 0.6% increase in the weekly rate of emergency room visits for upper respiratory infections for every 10 $\mu g/m^3$ increase in the weekly-averaged PM_{10} concentration. Studying more susceptible age classes, as elder people or children, the percentage of hospital admissions raise to 2-5% (Davila Cordova et al., 2020; Luong et al., 2017). Considering a wide population consisting of more than 300,000 individuals, significant positive associations between $PM_{2.5}$ and pneumonia/influenza deaths were observed for never-smokers, which resulted more susceptible to PM

exposure than former or current smokers (Pope III et al., 2004). This observation can also be extended to infants and children, whose exposure to PM has shown under-development of the lungs and consequently promotes an increased susceptibility to infections (Brugha and Grigg, 2014).

Several studies correlated influenza cases to PM exposure, comparing different years it was observed that occurrence of high $PM_{2.5}$ levels was associated with higher influenza peaks and with exacerbation of its symptoms (Liang et al., 2014). Recently, Croft et al. (2019) have evaluated the incidence of influenza measuring the number of visits to emergency room in hospital, and found that it was directly linked to the PM levels of the week before, with a 3-4% more cases in concomitance with an increase in PM concentration. Feng et al. (2016) showed a correlation between $PM_{2.5}$ concentrations and influenza-like illnesses only in the period of the year when flu has its natural spread, while at the non-flu season the two events were not linked. This may be imputed to the infectivity of the virus and the meteorological conditions that favoured negative conditions in the airways, as body cooling and drying of the respiratory tract. It was also observed that other air pollutants can contribute to increased susceptibility to acute influenza, as gaseous pollutants such as NO_2 and SO_2 (Liu et al., 2019). Indeed, as aforementioned, high PM levels are often observed during winter months with strong atmospheric stability conditions; this situation promotes the build-up of gaseous pollutants and PM emitted at ground level thus generating a very complex pollution cocktail so that its relationship with health outcomes is not straightforward.

To understand the relationship between PM, respiratory viruses, and the onset of pathological conditions, it is necessary to explore the molecular mechanisms of the immune system inside the airways and the detrimental effects exerted by PM. The study of cellular and molecular mechanisms is only possible under laboratory conditions, where the exposure of animals or cells to non-biological PM and BioPM (fungi, bacteria, or viruses) has to be led consequently or in parallel, but always separately.

A primary event that favours the spread of viruses in the airway system after PM inhalation, is the damage of the defensive barriers as the tracheal cilia and mucociliary epithelium. These structures can undergo remodelling and loss of efficiency, slowing or diminishing the clearance capacity (Ghio, 2014; Liu et al.,

2019; Ni et al., 2015; Oh et al., 2011), while goblet cells, normally able to secrete the protective layer of mucus against ultrafine particles, can suffer from cytotoxicity (Yang et al., 2020).

Among the factors that compromise the normal immunological defence are damage of alveolar macrophages (AM) (Donaldson and Tran, 2002; Liu et al., 2019), increase of permeability in airway epithelial cells (Li et al., 1996), alteration of T cell populations (Lee et al., 2014), and impairment of natural killer (NK) cells response (Grahame et al., 2014). AM are involved in the inhibition of viruses spreading in the lower respiratory tract (Becker et al., 2010); thus, the detrimental action of PM on these cells can favour the development of infections. Exposure to PM is known to decrease AM viability, indeed Michael et al. (2013), using a murine *in vitro* model, observed a significant reduction in the survival rate of AM after 48 hours of treatment with 50 μg/ml of both urban and rural PM_{10}. Moreover, PM and especially ultrafine particles (Macnee and Donaldson, 2003) can decrease the phagocytic activity of AM (Ghio, 2014; Ni et al., 2015) by blocking the release of O_2^- and other ROS (Castranova et al., 2001; Sawyer et al., 2010). Another anti-viral action that depends on AM is the secretion of cytokines to recall adaptive immunity (Castranova et al., 2001); IL-1β and TNF-α mediate chemotaxis and leukocyte activation, while IL-6 is important in antibody response (Ramshaw et al. 1997). It was demonstrated, both in human and animal models, that the production of cytokines and the consequential activation of the adaptive response can be compromised after exposure to PM, increasing individual susceptibility to infections (Becker et al., 2010; Ma et al., 2017).

For what concerns T cells responses, it was demonstrated that $PM_{2.5}$ favours an imbalance between the different T cells populations. Normally, primary T helper type 1 (Th1) cells are appointed to the protection against infectious agents, while the fraction of T cells known as T regs is devoted to immunosuppression (Lee et al., 2014; Saravia et al., 2014). After $PM_{2.5}$ exposure, an elevated production of T regs and inhibition of the generation of new Th1 has been observed (Jaligama et al., 2017; Matthews et al., 2014). The molecular mechanisms underlying this issue were studied by Jaligama et al. (2017) in a mouse model: animals exposed to PM showed an increase in the secretion of the immunoregulatory cytokine IL-10, which is able to decrease the activity of Th1 and stimulate T regs population, leading to severe outcomes

following influenza infection. The combination of these two factors leads to an incorrect response to pathogens, as influenza virus or *Klebsiella pneumoniae*, as demonstrated in mice (Saravia et al., 2014).

Another group of cells involved in the immune response against viruses is NK cells. These cells have the ability to kill virus-infected cells, but can also connect innate and adaptive immunity releasing cytokines (Grahame et al., 2014; Müller et al., 2013). The immunosuppression following PM exposure was demonstrated *in vitro* by Müller et al. (2013), who observed how PM impaired the formation and release of granzyme B and perforin, the two major cytotoxic enzymes of NK cells. Another mechanism that can impair the action of NK cells against viral infections is the suppression of IP-10, a chemoattractant for NK cells present in infected tissues, exerted by wood smoke particles and diesel exhaust particles (DEP) (Rebuli et al., 2019).

A peculiar pathway involved in the antiviral defence of respiratory immune system is the one leading to the production of interferon (IFN) family proteins - in particular IFN-γ - which are stimulatory of the antiviral state. Normally, their synthesis follows the activation of T and NK cells or the recognition of infected cells (Goodbourn et al., 2000). After exposure to $PM_{2.5}$ collected at urban sites, the production of IFN-γ is reduced, allowing enhanced viral replication and leading to a lower defence of the immune system (Ni et al., 2015). Using a murine model, Lambert et al. (2003) observed that exposure to $PM_{2.5}$ determines a reduced expression of IFN-γ, increasing individual susceptibility to RSV infections. Castranova et al. (2001) focused on the burden of PM carbonaceous components, demonstrating the specific ability of organic compounds adsorbed on DEP to interfere in the production of IFN-γ. IFN-β is also involved in the innate immune response. The exposure to high doses of PM_{10} reduces its transcription, along with the activation of other antiviral genes, while it stimulates viral replication, as demonstrated by Mishra et al. (2020) in the study of influenza for a 1:1 ratio between extracted PM_{10} and culture media.

Another detrimental aspect of PM exposure is the generation of oxidative stress. Indeed, this condition can trigger the spread of infections in the airways, making lung cells more susceptible to pathogens (Grigg, 2009). Jaligama et al. (2017) reported the presence of persistent radical species in atmospheric PM; these

radicals were studied for their ability to promote a temporal immunosuppressive state and enhance the persistence of influenza. The molecular mechanism is still unclear: it is possible that the oxidative stress inhibits GSH (glutathione) and this block contributes to the enhancement of the viral replication in the respiratory system (Lee et al., 2014). Michael et al. (2013) used a human *in vitro* model to explore these mechanisms and showed significantly decreased levels of GSH and a reduced activity of its synthesis enzymes, as SOD (superoxide dismutase), after exposure to PM_{10} concentrations above 50 μg/ml.

To summarize, in this section the association between PM exposure and the onset of infections was presented in terms of factors affecting this relationship, types of infectious diseases mostly reported as related to PM (respiratory viral infections and in particular influenza), and detrimental effects of PM causing peculiar molecular mechanisms of the immune system in the respiratory tract (damage of mechanical defensive barriers and AM, alteration of T and NK cells action and innate immune response, and generation of oxidative stress).

5. BioPM: A possible source of infectious diseases

As aforementioned, BioPM comprises a wide range of pathogens that can undermine individuals' health in peculiar ways. Exposure to BioPM consisting in pollens is well-known to cause allergic reactions in genetically predisposed individuals, with symptoms ranging from coughing and throat irritation, to asthma or hypersensitivity pneumonitis (Menetrez et al., 2009), while exposure to endotoxin from gram negative bacteria can induce a severe inflammatory state (Shen et al., 2019).

In ambient conditions, microorganisms such as fungal spores, bacteria, and viruses can be found airborne (see e.g. Cao et al. 2014; Y. Zhao et al. 2019b); atmospheric particles can damage mucosal barriers and mucociliary clearance so that airborne microorganisms can directly and more easily penetrate into the airways (D'Amato, 2002). About the interaction between viruses and PM in ambient conditions, a recent theoretical study by Belosi et al. (2021) has shown that the probability of coagulation between a virus-laden particle and another aerosol particle in the air is extremely low for the accumulation (100-800 nm) and coarse (> 2.5 μm) aerosol mode.

Many atmospheric factors can influence the presence of airborne microorganisms in ambient air, as temperature, relative humidity, wind speed, and solar radiation, even though the effect of these parameters on the release, growth, viability, and distribution of microorganisms is not straightforward (e.g. Alghamdi et al., 2014; Haas et al., 2013; Zhai et al., 2018). Diurnal variations have been observed: sunrise and sunset are associated with a rise in concentration of airborne microorganisms, while intense daylight is related to its decrease (Zhai et al., 2018); this diurnal pattern is driven by both the atmospheric mixing layer height, that is linked to solar radiation, and emissions from human activities.

The influence of temperature depends on the type of microorganism but also on the interaction with other meteorological parameters. The concentrations of airborne fungi and bacteria have often been found to positively correlate with temperature (Zhai et al., 2018), even though T>24 °C generally decreases the survival of airborne bacteria (Tang, 2009). Viruses survival is negatively affected by high temperature, which can alter viral proteins and genome (Tang, 2009; Zhai et al., 2018).

The effect of relative humidity (RH) on airborne microorganisms is even less clear. Zhai et al (2018) reviewed a number of past studies reporting contrasting results i.e. some of them saying that low RH levels promoted microbial release and others asserting that high RH was beneficial to bacterial release and growth but it might also negatively impact on bacteria viability. High RH conditions also favours deposition processes because it increases weight and size of microbial particles. As far as viruses are concerned, they show the minimal survival at intermediate RH values (40-70%), with different behaviours exhibited by viruses with lipid envelopes (such as influenza viruses, coronaviruses, RSV, parainfluenza viruses, measles, rubella, varicella zoster virus), which tend to survive longer at RH<20-30%, and non-lipid enveloped viruses (e.g. respiratory adenoviruses and rhinoviruses) whose survival is maximum at higher RH (70-90%) (Tang et al., 2009; and references therein).

Literature studies stated that the increase of wind speed can positively influence the presence of microorganisms in the air, resuspending a large amount of biological material: bacteria were observed spreading up to 50 km in distance, while viruses travel much more and can cross geographical barriers, as observed for the English channel or the Taiwan strait (Jones and Harrison, 2004; Löndahl, 2014).

Nevertheless, high wind speed also exerts a strong dilution effect on the atmosphere: this can be the reason behind the weak or lack of correlation between wind speed and microbial concentration in the atmosphere found by several studies (Zhai et al., 2018).

Solar radiation, and especially its ultraviolet (UV) component, is agreed to be harmful to both bacteria and viruses (Tang, 2009). In their recent study, Schuit et al. (2020) demonstrated that the biological decay rate (i.e. rate of infectivity loss) of influenza A virus (H1N1) increases with increasing duration and intensity of sunlight, independently of RH.

The effect of other factors such as gaseous pollutants on microorganisms concentration and viability in the atmosphere is poorly understood, also because of the concomitant influence of meteorological parameters (Soleimani et al., 2020; Tang, 2009; Zhai et al., 2018).

It is worthy to note that many literature studies investigated health outcomes and particularly the occurrence of infectious diseases following high PM concentration episodes due e.g. to the transport of particular aerosol types as during desert dust storms (Soleimani et al., 2020). Nevertheless, as far as the authors know, the effect of specific aerosol components on an increased presence of microorganisms in the atmosphere, which could have caused the observed health impacts, has not been assessed yet.

The concentration of different BioPM components vary according to the season, location and climate; generating specific compositions in each region of the world (Alghamdi et al., 2014; Schwarze et al., 2006). BioPM composition depends also on the human community, which can influence the concentration or the presence of some species (Fang et al., 2007, 2005; Shen et al., 2019). As an example, Shen et al. (2019) observed that Chinese urban and rural BioPM is composed by different bacterial genera, with a specificity of more than 85% at each site: in Bejing the most abundant genus was *Lactococcus* (49.5%), that accounted only for 1% of the total abundance at the rural site of Wangdu, where predominated *Enterococcus* (65%) and other soil-derived genera.

The recent outbreak of the SARS-CoV-2 pandemic and the possibility for this virus to exist in ambient air as airborne and associated with non-biological PM have gained interest in the scientific community worldwide

and the debate about the mechanisms of transmission is still going on (Asadi et al., 2020; Belosi et al., 2021; Buonanno et al., 2020; Drossinos and Stilianakis, 2020; Jiang et al., 2020; Morawska and Cao, 2020; Niazi et al., 2020). Scientific literature on viral BioPM is still scarce, probably because of the inefficiency of the current measurement methods (Löndahl, 2014). It is reported that the identification of viral dsDNA (double stranded DNA) in PM samples is possible with few limitations, while RNA strains are more challenging to recognize, due to the scarce material available for reverse transcription and further analyses (Cao et al., 2014). It has to be noted that the detection of respirable PM containing RNA traces does not mean that the virus is viable or infectious (Belosi et al., 2021; Niazi et al., 2020). As far as the authors know, up to date none have demonstrated whether the viruses were attached to or simply mixed with other particles or different aerosol components which are collected all together. As already mentioned, Belosi et al. (2021) investigated the probability that SARS-CoV-2 virus-laden aerosol coagulate with pre-existing atmospheric PM: it resulted to be negligible and not relevant for the dynamic of the viral particles.

The presence of BioPM, and particularly viruses, is also related to some anthropogenic activities as agricultural practice, farming, or sewage treatment (Jones and Harrison, 2004; Kim et al., 2018; Mbareche et al., 2019). Wastewater treatment centres are one of the most recognized sources of occupational risk of contagions: pathogens that affect the gastroenteric system, as noroviruses or rotaviruses, and adenoviruses or rhinoviruses which are responsible for the common cold have been found (Brisebois et al., 2018).

Adenoviruses, due to their wide diffusion, are considered an indicator of the population's contamination; adenoviruses of major interest are B and C groups (HAdV-B, HAdV-C), which give rise to respiratory infections. These were found to be the most abundant among adenoviruses in different sites of the US and in Israel, covering almost 92% of the total amount (Bibby and Peccia, 2013), and HAdV-C was also identified as the most prevalent virus found in PM_{10} and $PM_{2.5}$ samples during heavy smog events in Beijing (Cao et al., 2014). Concerning farm workers, the contact with infected animal secretions and the material resuspended in air can be a source of contagion (Jones and Harrison, 2004). As an example, influenza A diffusion in Chinese pig farms, studied by Anderson et al. (2016), resulted in an infection rate of one out of five workers. In contrast, other occupations as biohazard material handling or irrigation practices do not

seem to increase the risk of infection of workers (Mirskaya and Agranovski, 2018). Another viral group that is widely diffused is the whole of influenza viruses. These can infect both animals and humans and are likely to transmit cross-species, increasing their possibility to spread worldwide (Chan et al., 2015; Li et al., 2019; Ren et al., 2016).

Several papers have observed an increase of RSV infections with the rise of PM concentrations. This virus mainly affects children, determining symptoms similar to common cold and aggravation of pre-existing asthma (Hackett et al., 2011; Mirsaeidi et al., 2016). In Northern Italy it was shown how an acute exposure to PM_{10} and $PM_{2.5}$ resulted in increased RSV positive detections (Carugno et al., 2018; Vandini et al., 2013). To corroborate epidemiological data, *in vitro* studies were conducted to explore the survival rate and infectivity of RSV present in PM_{10} samples; as an example, Cruz-Sanchez et al. (2013) demonstrated an extended survival time of the virus in the air and an increased ability in infecting airway epithelial cells when RSV co-exists with carbonaceous aerosol compared to virus alone, leading to a higher inflammatory response, with a great release of IL-8 and IL-6 cytokines.

This section focused on some factors affecting the fate of airborne microorganisms and specifically we summarized results about the role of meteorological parameters and human communities. In particular, the authors focused on viral BioPM, highlighting how its presence in the atmosphere has been related to some anthropogenic activities (e.g. wastewater treatment, agricultural practices, and farming) that were found to be sources of noroviruses, rotaviruses, adenoviruses, rhinoviruses, influenza viruses, and RSV.

6. Perspectives and conclusions

The recent outbreak of the new coronavirus, SARS-CoV-2, has conveyed many research efforts and resources worldwide into the study of the molecular mechanisms leading to the infection and the causes of the viral diffusion among different countries. A very argued and controversial topic is the airborne transmission of the virus as well as the possible role of air pollution and PM, in particular, in the spread of COVID-19. Many issues are still open and further studies are mandatory to elucidate the probability of virus spreading and its viability and lifetime in locations with different loading and cocktail of pollutants, various

atmospheric conditions as well as number of inhabitants and population lifestyle. The authors would like also to underline that in a PM sample, any airborne aerosol is collected on the same filter and it is practically impossible to say if e.g. a BioPM component (e.g. a virus or bacteria) was natively a single particle in the atmosphere or was attached to another pre-existing particle. This is a key point which can explain observed relationships between PM and pathogens which are often misunderstood while being mainly driven by a co-existence in the same sample.

In this review, we have described how exposure to PM can contribute to lung infections. The comprehension of the link between PM and pathogens is necessary to understand the outcomes on human health. We illustrated two different ways in which PM can threaten individuals' health facilitating respiratory infections: the increase of susceptibility towards pathogens by disrupting the lung immune system, and the presence of pathogens in air (BioPM) as a possible source of infectious diseases.

Future scientific research should focus on a better understanding of the effects of BioPM on respiratory health and the mechanisms affecting its diffusion based on a multi-disciplinary approach, which is mandatory due to the complexity of the topic.

Authors contribution

E.N. and S.V. equally contributed in collecting the literary material and writing the manuscript. G.M., E.C., and R.V. revised and edited the work. All the authors have read and approved the final manuscript.

Funding

This work has been funded by the Italian Ministry of the University under the PRIN2017 RHAPS project (grant number: 2017MSN7M8).

Conflict of interest

The authors declare no conflict of interest in this work.

References

Ahmed, C.M.S., Yang, J., Chen, J.Y., Jiang, H., Cullen, C., Karavalakis, G., Lin, Y.H., 2020. Toxicological responses in human airway epithelial cells (BEAS-2B) exposed to particulate matter emissions from gasoline fuels with varying aromatic and ethanol levels. Sci. Total Environ. 706, 135732. https://doi.org/10.1016/j.scitotenv.2019.135732

Alghamdi, M.A., Shamy, M., Redal, M.A., Khoder, M., Awad, A.H., Elserougy, S., 2014. Microorganisms associated particulate matter: A preliminary study. Sci. Total Environ. 479–480, 109–116. https://doi.org/10.1016/j.scitotenv.2014.02.006

Amato, F., Alastuey, A., Karanasiou, A., Lucarelli, F., Nava, S., Calzolai, G., Severi, M., Becagli, S., Gianelle, V.L., Colombi, C., Alves, C., Custódio, D., Nunes, T., Cerqueira, M., Pio, C., Eleftheriadis, K., Diapouli, E., Reche, C., Minguillón, M.C., Manousakas, M.-I., Maggos, T., Vratolis, S., Harrison, R.M., Querol, X., 2016. AIRUSE-LIFE+: a harmonized PM speciation and source apportionment in five southern European cities. Atmos. Chem. Phys. 16, 3289–3309. https://doi.org/10.5194/acp-16-3289-2016

Anderson, B.D., Ma, M., Xia, Y., Wang, T., Shu, B., Lednicky, J.A., Ma, M.J., Lu, J., Gray, G.C., 2016. Bioaerosol sampling in modern agriculture: A novel approach for emerging pathogen surveillance? J. Infect. Dis. https://doi.org/10.1093/infdis/jiw180

Asadi, S., Bouvier, N., Wexler, A.S., Ristenpart, W.D. Asadi, S., Bouvier, N., Wexler, A.S., Ristenpart, W.D., 2020. The coronavirus pandemic and aerosols : Does COVID-19 transmit via expiratory particles ? Aerosol Sci. Technol. 54, 635–638. https://doi.org/10.1080/02786826.2020.1749229

Becker, S., Soukup, J.M., Becker, S., Soukup, J.M., To, E., Air, U., Becker, S., Soukup, J.M., 2010. EXPOSURE TO URBAN AIR PARTICULATES ALTERS THE MACROPHAGE-MEDIATED INFLAMMATORY RESPONSE TO RESPIRATORY VIRAL INFECTION PARTICULATES ALTERS THE MACROPHAGE-MEDIATED INFLAMMATORY RESPONSE TO EXPOSURE TO URBAN AIR PARTICULATES ALTERS THE MACROPHAGE-MEDIATED I 7394. https://doi.org/10.1080/009841099157539

Bell, M.L., Dominici, F., Ebisu, K., Zeger, S.L., Samet, J.M., 2007. Spatial and Temporal Variation in PM2.5 Chemical Composition in the United States for Health Effects Studies 115, 989–995. https://doi.org/10.1289/ehp.9621

Belosi, F., Conte, M., Gianelle, V., Santachiara, G., Contini, D., 2021. On the concentration of SARS-CoV-2 in outdoor air and the interaction with pre-existing atmospheric particles. Environ. Res. 193, 110603.

https://doi.org/10.1016/j.envres.2020.110603

Bhattarai, H., Saikawa, E., Wan, X., Zhu, H., Ram, K., Gao, S., Kang, S., Zhang, Q., Zhang, Y., Wu, G., Wang, X., Kawamura, K., Fu, P., Cong, Z., 2019. Levoglucosan as a tracer of biomass burning: Recent progress and perspectives. Atmos. Res. 220, 20–33. https://doi.org/10.1016/j.atmosres.2019.01.004

Bibby, K., Peccia, J., 2013. Prevalence of respiratory adenovirus species B and C in sewage sludge. Environ. Sci. Process. Impacts. https://doi.org/10.1039/c2em30831b

Boucher, O., 2015. Atmospheric Aerosols - Properties and Climate Impacts. Springer Netherlands, Dordrecht. https://doi.org/10.1007/978-94-017-9649-1

Brisebois, E., Veillette, M., Dion-Dupont, V., Lavoie, J., Corbeil, J., Culley, A., Duchaine, C., 2018. Human viral pathogens are pervasive in wastewater treatment center aerosols. J. Environ. Sci. (China). https://doi.org/10.1016/j.jes.2017.07.015

Brown, J.S., Gordon, T., Price, O., Asgharian, B., 2013. Thoracic and respirable particle definitions for human health risk assessment. Part. Fibre Toxicol. 10, 12. https://doi.org/10.1186/1743-8977-10-12

Brugha, R., Grigg, J., 2014. Urban air pollution and respiratory infections. Paediatr. Respir. Rev. 15, 194–199. https://doi.org/10.1016/j.prrv.2014.03.001

Bui, V.K.H., Moon, J.-Y., Chae, M., Park, D., Lee, Y.-C., 2020. Prediction of Aerosol Deposition in the Human Respiratory Tract via Computational Models: A Review with Recent Updates. Atmosphere (Basel). 11, 137. https://doi.org/10.3390/atmos11020137

Buonanno, G., Morawska, L., Stabile, L., 2020. Quantitative assessment of the risk of airborne transmission of SARS-CoV-2 infection: Prospective and retrospective applications. Environ. Int. 145, 106112. https://doi.org/10.1016/j.envint.2020.106112

Calvo, A.I., Alves, C., Castro, A., Pont, V., Vicente, A.M., Fraile, R., 2013. Research on aerosol sources and chemical composition: Past, current and emerging issues. Atmos. Res. 120–121, 1–28. https://doi.org/10.1016/j.atmosres.2012.09.021

Cao, C., Jiang, W., Wang, B., Fang, J., Lang, J., Tian, G., Jiang, J., Zhu, T.F., 2014. Inhalable microorganisms in Beijing's

PM2.5 and PM10 pollutants during a severe smog event. Environ. Sci. Technol. 48, 1499–1507. https://doi.org/10.1021/es4048472

Carinanos, P., Galan, C., Alcazar, P., Dominguez, E., 2007. Analysis of solid particulate matter suspended in the air of Cordoba, southwestern Spain. Ann Agric Env. Med. 14, 219–224.

Carugno, M., Dentali, F., Mathieu, G., Fontanella, A., Mariani, J., Bordini, L., Milani, G.P., Consonni, D., Bonzini, M., Bollati, V., Pesatori, A.C., 2018. PM10 exposure is associated with increased hospitalizations for respiratory syncytial virus bronchiolitis among infants in Lombardy, Italy. Environ. Res. https://doi.org/10.1016/j.envres.2018.06.016

Cassee, F.R., Héroux, M.E., Gerlofs-Nijland, M.E., Kelly, F.J., 2013. Particulate matter beyond mass: Recent health evidence on the role of fractions, chemical constituents and sources of emission. Inhal. Toxicol. 25, 802–812. https://doi.org/10.3109/08958378.2013.850127

Castranova, V., Ma, J.Y.C.J.K.H., Yang, H.M., Antonini, J.M., Butterworth, L., Barger, M.W., Roberts, J., Ma, J.Y.C.J.K.H., 2001. Effect of exposure to diesel exhaust particles on the susceptibility of the lung to infection. Environ. Health Perspect. 109, 609–612. https://doi.org/10.2307/3454678

Chan, J.F.W., To, K.K.W., Chen, H., Yuen, K.Y., 2015. Cross-species transmission and emergence of novel viruses from birds. Curr. Opin. Virol. https://doi.org/10.1016/j.coviro.2015.01.006

Chen, J., Li, C., Ristovski, Z., Milic, A., Gu, Y., Islam, M.S., Wang, S., Hao, J., Zhang, H., He, C., Guo, H., Fu, H., Miljevic, B., Morawska, L., Thai, P., LAM, Y.F., Pereira, G., Ding, A., Huang, X., Dumka, U.C., 2017. A review of biomass burning: Emissions and impacts on air quality, health and climate in China. Sci. Total Environ. 579, 1000–1034. https://doi.org/10.1016/j.scitotenv.2016.11.025

Ching, J., Kajino, M., 2018. Aerosol mixing state matters for particles deposition in human respiratory system. Sci. Rep. 8, 8864. https://doi.org/10.1038/s41598-018-27156-z

Ciencewicki, J., Jaspers, I., Ciencewicki, J., 2008. Air Pollution and Respiratory Viral Infection 8378. https://doi.org/10.1080/08958370701665434

Clifford, H.D., Perks, K.L., Zosky, G.R., 2015a. Science of the Total Environment Geogenic PM 10 exposure exacerbates

responses to in fl uenza infection. Sci. Total Environ. 533, 275–282. https://doi.org/10.1016/j.scitotenv.2015.07.001

Clifford, H.D., Perks, K.L., Zosky, G.R., 2015b. Geogenic PM 10 exposure exacerbates responses to in fluenza infection. Sci. Total Environ. 533, 275–282. https://doi.org/10.1016/j.scitotenv.2015.07.001

Corsini, E., Budello, S., Marabini, L., Galbiati, V., Piazzalunga, A., Barbieri, P., Cozzutto, S., Marinovich, M., Pitea, D., Galli, C.L., 2013. Comparison of wood smoke PM2.5 obtained from the combustion of FIR and beech pellets on inflammation and DNA damage in A549 and THP-1 human cell lines. Arch. Toxicol. https://doi.org/10.1007/s00204-013-1071-z

Croft, D.P., Zhang, W., Lin, S., Thurston, S.W., Hopke, P.K., Masiol, M., Squizzato, S., van Wijngaarden, E., Utell, M.J., Rich, D.Q., 2019. The association between respiratory infection and air pollution in the setting of air quality policy and economic change. Ann. Am. Thorac. Soc. 16, 321–330. https://doi.org/10.1513/AnnalsATS.201810-691OC

Cruz-Sanchez, T.M., Haddrell, A.E., Hackett, T.L., Singhera, G.K., Marchant, D., Lekivetz, R., Meredith, A., Horne, D., Knight, D.A., Van Eeden, S.F., Bai, T.R., Hegele, R.G., Dorscheid, D.R., Agnes, G.R., 2013. Formation of a stable mimic of ambient particulate matter containing viable infectious respiratory syncytial virus and its dry-deposition directly onto cell cultures. Anal. Chem. https://doi.org/10.1021/ac302174y

D'Amato, G., 2002. Environmental urban factors (air pollution and allergens) and the rising trends in allergic respiratory diseases. Allergy 57, 30–33. https://doi.org/10.1034/j.1398-9995.57.s72.5.x

Davila Cordova, J.E., Tapia Aguirre, V., Vasquez Apestegui, V., Ordoñez Ibarguen, L., Vu, B.N., Steenland, K., Gonzales Rengifo, G.F., 2020. Association of PM2.5 concentration with health center outpatient visits for respiratory diseases of children under 5 years old in Lima, Peru. Environ. Heal. A Glob. Access Sci. Source. https://doi.org/10.1186/s12940-020-0564-5

Deng, Q., Deng, L., Miao, Y., Guo, X., Li, Y., 2019. Particle deposition in the human lung: Health implications of particulate matter from different sources. Environ. Res. 169, 237–245. https://doi.org/10.1016/j.envres.2018.11.014

Denier van der Gon, H.A.C., Gerlofs-Nijland, M.E., Gehrig, R., Gustafsson, M., Janssen, N., Harrison, R.M., Hulskotte, J.,

Johansson, C., Jozwicka, M., Keuken, M., Krijgsheld, K., Ntziachristos, L., Riediker, M., Cassee, F.R., 2013. The Policy Relevance of Wear Emissions from Road Transport, Now and in the Future—An International Workshop Report and Consensus Statement. J. Air Waste Manage. Assoc. 63, 136–149. https://doi.org/10.1080/10962247.2012.741055

Després, V., Huffman, J.A., Burrows, S.M., Hoose, C., Safatov, A., Buryak, G., Fröhlich-Nowoisky, J., Elbert, W., Andreae, M., Pöschl, U., Jaenicke, R., 2012. Primary biological aerosol particles in the atmosphere: a review. Tellus B Chem. Phys. Meteorol. 64, 15598. https://doi.org/10.3402/tellusb.v64i0.15598

Devouassoux, G., Saxon, A., Metcalfe, D.D., Prussin, C., Colomb, M.G., Brambilla, C., Diaz-Sanchez, D., 2002. Chemical constituents of diesel exhaust particles induce IL-4 production and histamine release by human basophils. J. Allergy Clin. Immunol. 109, 847–853. https://doi.org/10.1067/mai.2002.122843

Dockery, D.W., Pope III, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris Jr, B.G., Speizer, F.., 1993. An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329, 1753–1759. https://doi.org/10.1056/NEJM199312093292401

Donaldson, K., Tran, C.L., 2002. Inflammation caused by particles and fibers. Inhal. Toxicol. 14, 5–27. https://doi.org/10.1080/08958370175333[illegible]613

Donaldson, K., Tran, L., Jimenez, L.A., Duffin, R., Newby, D.E., Mills, N., MacNee, W., Stone, V., 2005. Combustion-derived nanoparticles: A review of their toxicology following inhalation exposure. Part. Fibre Toxicol. 2, 1–14. https://doi.org/10.1186/1743-8977-2-10

Drinker, P., 1953. Deaths during the severe fog in London and environs, Dec. 5 to 9, 1952. A. M. A. Arch. Ind. Hyg. Occup. Med.

Drossinos, Y., Stilianakis, N.I., 2020. What aerosol physics tells us about airborne pathogen transmission. Aerosol Sci. Technol. 0, 1–5. https://doi.org/10.1080/02786826.2020.1751055

Fang, Z., Ouyang, Z., Hu, L., Wang, X., Zheng, H., Lin, X., 2005. Culturable airborne fungi in outdoor environments in Beijing, China. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2005.01.032

Fang, Z., Ouyang, Z., Zheng, H., Wang, X., Hu, L., 2007. Culturable airborne bacteria in outdoor environments in Beijing,

China. Microb. Ecol. https://doi.org/10.1007/s00248-007-9216-3

Feng, C., Li, J., Sun, W., Zhang, Y., Wang, Q., 2016. Impact of ambient fine particulate matter (PM2.5) exposure on the risk of influenza-like-illness: A time-series analysis in Beijing, China. Environ. Heal. A Glob. Access Sci. Source 15, 1–12. https://doi.org/10.1186/s12940-016-0115-2

Fröhlich-Nowoisky, J., Kampf, C.J., Weber, B., Huffman, J.A., Pöhlker, C., Andreae, M.O., Lang-Yona, N., Burrows, S.M., Gunthe, S.S., Elbert, W., Su, H., Hoor, P., Thines, E., Hoffmann, T., Després, V.R., Pöschl, U., 2016. Bioaerosols in the Earth system: Climate, health, and ecosystem interactions. Atmos. Res. 182, 346–376. https://doi.org/10.1016/j.atmosres.2016.07.018

Fuzzi, S., Baltensperger, U., Carslaw, K., Decesari, S., Denier Van Der Gon, H., Facchini, M.C., Fowler, D., Koren, I., Langford, B., Lohmann, U., Nemitz, E., Pandis, S., Riipinen, I., Rudich, Y., Schaap, M., Slowik, J.G., Spracklen, D. V., Vignati, E., Wild, M., Williams, M., Gilardoni, S., 2015. Particulate matter, air quality and climate: Lessons learned and future needs. Atmos. Chem. Phys. 15, 8217–8299. https://doi.org/10.5194/acp-15-8217-2015

Gao, Y., Ji, H., 2018. Microscopic morphology and seasonal variation of health e ff ect arising from heavy metals in PM2.5 and PM10 : One-year measurement in a densely populated area of urban Beijing. Atmos. Res. 212, 213–226. https://doi.org/10.1016/j.atmosres.2018.04.027

Ghio, A.J., 2014. Particle exposures and infections. Infection 42, 459–467. https://doi.org/10.1007/s15010-014-0592-6

Ginoux, P., Prospero, J.M., Gill, T.E., Hsu, N.C., Zhao, M., 2012. Global-scale attribution of anthropogenic and natural dust sources and their emission rates based on MODIS Deep Blue aerosol products. Rev. Geophys. 50. https://doi.org/10.1029/2012RG000388

Goodbourn, S., Didcock, L., Randall, R.E., 2000. Interferons: Cell signalling, immune modulation, antiviral responses and virus countermeasures. J. Gen. Virol. 81, 2341–2364. https://doi.org/10.1099/0022-1317-81-10-2341

Grahame, T.J., Klemm, R., Schlesinger, R.B., 2014. Public health and components of particulate matter: The changing assessment of black carbon. J. Air Waste Manag. Assoc. 64, 620–660. https://doi.org/10.1080/10962247.2014.912692

Grigg, J., 2009. Particulate matter exposure in children: Relevance to chronic obstructive pulmonary disease. Proc. Am.

Thorac. Soc. 6, 564–569. https://doi.org/10.1513/pats.200905-026RM

Groulx, N., Urch, B., Duchaine, C., Mubareka, S., Scott, J.A., 2018. The Pollution Particulate Concentrator (PoPCon): A platform to investigate the effects of particulate air pollutants on viral infectivity. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2018.02.118

Gualtieri, M., Øvrevik, J., Mollerup, S., Asare, N., Longhin, E., Dahlman, H.J., Camatini, M., Holme, J.A., 2011. Airborne urban particles (Milan winter-PM2.5) cause mitotic arrest and cell death: Effects on DNA, mitochondria, AhR binding and spindle organization. Mutat. Res. - Fundam. Mol. Mech. Mutagen. 713, 18–31. https://doi.org/10.1016/j.mrfmmm.2011.05.011

Haas, D., Galler, H., Luxner, J., Zarfel, G., Buzina, W., Friedl, H., Marth, E., Habler, J., Reinthaler, F.F., 2013. The concentrations of culturable microorganisms in relation to particulate matter in urban air. Atmos. Environ. 65, 215–222. https://doi.org/10.1016/j.atmosenv.2012.10.031

Hackett, T.L., Singhera, G.K., Shaheen, F., Hayden, P., Jackson, G.R., Hegele, R.G., Van Eeden, S., Bai, T.R., Dorscheid, D.R., Knight, D.A., 2011. Intrinsic phenotypic differences of asthmatic epithelium and its inflammatory responses to respiratory syncytial virus and air pollution. Am. J. Respir. Cell Mol. Biol. 45, 1090–1100. https://doi.org/10.1165/rcmb.2011-0031OC

Hand, J.L., Schichtel, B.A., Pitchford, M., Malm, W.C., Frank, N.H., 2012. Seasonal composition of remote and urban fine particulate matter in the United States. J. Geophys. Res. Atmos. 117, 1–22. https://doi.org/10.1029/2011JD017122

Healy, D., Sodeau, J., 2012. Secure Archive For Environmental Research Data [WWW Document]. Anal. Dev. Occur. Biol. Chem. aerosols. URL http://erc.epa.ie/safer/resource?id=c5efd96e-e353-11e2-8c2d-005056ae0019 (accessed 7.10.20).

Hinds, W.C., 1999. Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles, 2nd Edition. John Wiley and sons.

Hofmann, W., 2011. Modelling inhaled particle deposition in the human lung—A review. J. Aerosol Sci. 42, 693–724. https://doi.org/10.1016/j.jaerosci.2011.05.007

Horne, B.D., Joy, E.A., Hofmann, M.G., Gesteland, P.H., Cannon, J.B., Lefler, J.S., Blagev, D.P., Kent Korgenski, E., Torosyan, N., Hansen, G.I., Kartchner, D., Arden Pope, C., 2018. Short-term elevation of fine particulate matter air pollution and acute lower respiratory infection. Am. J. Respir. Crit. Care Med. 198, 759–766. https://doi.org/10.1164/rccm.201709-1883OC

Hueglin, C., Gehrig, R., Baltensperger, U., Gysel, M., Monn, C., Vonmont, H., 2005. Chemical characterisation of PM2.5 , PM10 and coarse particles at urban , near-city and rural sites in Switzerland. Atmos. Environ. 39, 637–651. https://doi.org/10.1016/j.atmosenv.2004.10.027

IARC, 2016. Outdoor Air Pollution - IARC nonographs on the evaluation of carcinogenic risks to humans; volume 109.

ICRP, 1994. Human respiratory tract model for radiological protection, ICRP Publication 66. Ann. ICRP.

Jaakkola, K., Saukkoriipi, A., Jokelainen, J., Juvonen, R., Kauppila, J., Vainio, O., Ziegler, T., 2014. Decline in temperature and humidity increases the occurrence of influenza in cold climate 1–8.

Jaenicke, R., 2005. Abundance of Cellular Material and Proteins in the Atmosphere. Science (80-.). 308, 73–73. https://doi.org/10.1126/science.1106335

Jain, S., Sharma, S.K., Vijayan, N., Mandal, T.K., 2020. Seasonal characteristics of aerosols (PM2.5 and PM10) and their source apportionment using PMF : A four year study over Delhi , India. Environ. Pollut. 262, 114337. https://doi.org/10.1016/j.envpol.2020.114337

Jaligama, S., Saravia, J., You, D., Yadav, N., Lee, G.I., Shrestha, B., Cormier, S.A., 2017. Regulatory T cells and IL10 suppress pulmonary host defense during early-life exposure to radical containing combustion derived ultrafine particulate matter. Respir. Res. 18, 1–14. https://doi.org/10.1186/s12931-016-0487-4

Jiang, J., Vincent Fu, Y., Liu, L., Kulmala, M., 2020. Transmission via aerosols: Plausible differences among emerging coronaviruses. Aerosol Sci. Technol. 54, 865–868. https://doi.org/10.1080/02786826.2020.1769020

Jones, A.M., Harrison, R.M., 2004. The effects of meteorological factors on atmospheric bioaerosol concentrations - A review. Sci. Total Environ. 326, 151–180. https://doi.org/10.1016/j.scitotenv.2003.11.021

Kim, K.H., Kabir, E., Jahan, S.A., 2018. Airborne bioaerosols and their impact on human health. J. Environ. Sci. (China) 67, 23–35. https://doi.org/10.1016/j.jes.2017.08.027

Kreyling, W.G., Semmler-Behnke, M., Seitz, J., Scymczak, W., Wenk, A., Mayer, P., Takenaka, S., Oberdrster, G., 2009. Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. Inhal. Toxicol. 21, 55–60. https://doi.org/10.1080/08958370902942517

Lambert, A.L., Trasti, F.S., Mangum, J.B., Everitt, J.I., 2003. Effect of preexposure to ultrafine carbon black on respiratory syncytial virus infection in mice. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfg031

Lee, G.I., Saravia, J., You, D., Shrestha, B., Jaligama, S., Hebert, V.Y., Dugas, T.R., Cormier, S.A., 2014. Exposure to combustion generated environmentally persistent free radicals enhances severity of influenza virus infection 1–10.

Li, X.Y., Gilmour, P.S., Donaldson, K., MacNee, W., 1996. Pro-inflammatory effect of particulate air pollution (PM10) in vivo and in vitro. Thorax 51, 1216–1222.

Li, Y.T., Linster, M., Mendenhall, I.H., Su, Y.C.F., Smith, G.J.D., 2019. Avian influenza viruses in humans: Lessons from past outbreaks. Br. Med. Bull. https://doi.org/10.1093/bmb/ldz036

Liang, Y., Fang, L., Pan, H., Zhang, K., Kan, H., Brook, J.R., Sun, Q., 2014. PM 2 . 5 in Beijing – temporal pattern and its association with influenza 1–8.

Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., AlMazroa, M.A., Amann, M., Anderson, H.R., Andrews, K.G., Aryee, M., Atkinson, C., Bacchus, L.J., Bahalim, A.N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M.L., Blore, J.D., Blyth, F., Bonner, C., Borges, G., Bourne, R., Boussinesq, M., Brauer, M., Brooks, P., Bruce, N.G., Brunekreef, B., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Bull, F., Burnett, R.T., Byers, T.E., Calabria, B., Carapetis, J., Carnahan, E., Chafe, Z., Charlson, F., Chen, H., Chen, J.S., Cheng, A.T.-A., Child, J.C., Cohen, A., Colson, K.E., Cowie, B.C., Darby, S., Darling, S., Davis, A., Degenhardt, L., Dentener, F., Des Jarlais, D.C., Devries, K., Dherani, M., Ding, E.L., Dorsey, E.R., Driscoll, T., Edmond, K., Ali, S.E., Engell, R.E., Erwin, P.J., Fahimi, S., Falder, G., Farzadfar, F., Ferrari, A., Finucane, M.M., Flaxman, S., Fowkes, F.G.R., Freedman, G., Freeman, M.K., Gakidou, E., Ghosh, S., Giovannucci, E., Gmel, G., Graham, K., Grainger, R., Grant, B., Gunnell, D., Gutierrez, H.R., Hall, W., Hoek, H.W., Hogan, A., Hosgood, H.D., Hoy, D., Hu, H., Hubbell, B.J., Hutchings, S.J., Ibeanusi, S.E., Jacklyn, G.L., Jasrasaria, R., Jonas, J.B., Kan, H., Kanis, J.A., Kassebaum, N., Kawakami, N., Khang, Y.-H., Khatibzadeh, S., Khoo, J.-P., Kok, C., Laden, F., Lalloo, R., Lan, Q., Lathlean, T., Leasher, J.L., Leigh, J., Li, Y., Lin,

J.K., Lipshultz, S.E., London, S., Lozano, R., Lu, Y., Mak, J., Malekzadeh, R., Mallinger, L., Marcenes, W., March, L., Marks, R., Martin, R., McGale, P., McGrath, J., Mehta, S., Memish, Z.A., Mensah, G.A., Merriman, T.R., Micha, R., Michaud, C., Mishra, V., Hanafiah, K.M., Mokdad, A.A., Morawska, L., Mozaffarian, D., Murphy, T., Naghavi, M., Neal, B., Nelson, P.K., Nolla, J.M., Norman, R., Olives, C., Omer, S.B., Orchard, J., Osborne, R., Ostro, B., Page, A., Pandey, K.D., Parry, C.D.H., Passmore, E., Patra, J., Pearce, N., Pelizzari, P.M., Petzold, M., Phillips, M.R., Pope, D., Pope, C.A., Powles, J., Rao, M., Razavi, H., Rehfuess, E.A., Rehm, J.T., Ritz, B., Rivara, F.P., Roberts, T., Robinson, C., Rodriguez-Portales, J.A., Romieu, I., Room, R., Rosenfeld, L.C., Roy, A., Rushton, L., Salomon, J.A., Sampson, U., Sanchez-Riera, L., Sanman, E., Sapkota, A., Seedat, S., Shi, P., Shield, K., Shivakoti, R., Singh, G.M., Sleet, D.A., Smith, E., Smith, K.R., Stapelberg, N.J.C., Steenland, K., Stöckl, H., Stovner, L.J., Straif, K., Straney, L., Thurston, G.D., Tran, J.H., Van Dingenen, R., van Donkelaar, A., Veerman, J.L., Vijayakumar, L., Weintraub, R., Weissman, M.M., White, R.A., Whiteford, H., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, W., Wilson, N., Woolf, A.D., Yip, P., Zielinski, J.M., Lopez, A.D., Murray, C.J.L., Ezzati, M., 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2224–2260. https://doi.org/10.1016/S0140-6736(12)61766-8

Liu, X., Li, Y., Qin, G., Zhu, Y., Li, X., Zhang, J., Zhao, Y., Hu, M., 2019. Effects of air pollutants on occurrences of influenza-like illness and laboratory-confirmed influenza in Hefei , China. Int. J. Biometeorol. 63, 51–60.

Löndahl, J., 2014. Bioaerosol Detection Technologies. Bioaerosol Detect. Technol. 41–42. https://doi.org/10.1007/978-1-4419-5582-1

Luong, L.M.T., Phung, D., Sly, P.D., Morawska, L., Thai, P.K., 2017. The association between particulate air pollution and respiratory admissions among young children in Hanoi, Vietnam. Sci. Total Environ. 578, 249–255. https://doi.org/10.1016/j.scitotenv.2016.08.012

Ma, J.H., Song, S.H., Guo, M., Zhou, J., Liu, F., Peng, L., Fu, Z.R., 2017. Long-term exposure to PM2.5 lowers influenza virus resistance via down-regulating pulmonary macrophage Kdm6a and mediates histones modification in IL-6 and IFN-β promoter regions. Biochem. Biophys. Res. Commun. 493, 1122–1128. https://doi.org/10.1016/j.bbrc.2017.09.013

Macnee, W., Donaldson, K., 2003. Mechanism of lung injury caused by PM 10 and ultrafine particles with special

reference to COPD 47–51. https://doi.org/10.1183/09031936.03.00403203

Madl, P., Majid, H., 2011. Lung deposition predictions of airborne particles and the emergence of contemporary diseases -Part II. theHealth 2, 101–107.

Majid, H., Madl, P., 2011. Lung deposition predictions of airborne particles and the emergence of contemporary diseases Part-I. theHealth 2, 51–56.

Marabini, L., Ozgen, S., Turacchi, S., Aminti, S., Arnaboldi, F., Lonati, G., Fermo, P., Corbella, L., Valli, G., Bernardoni, V., Dell'Acqua, M., Vecchi, R., Becagli, S., Caruso, D., Corrado, L.G., Marinovich, M., 2017. Ultrafine particles (UFPs) from domestic wood stoves: genotoxicity in human lung carcinoma A549 cells. Mutat. Res. - Genet. Toxicol. Environ. Mutagen. https://doi.org/10.1016/j.mrgentox.2017.06.00[illegible]

Matthews, N.C., Faith, A., Pfeffer, P., Lu, H., Kelly, F.J., Hawrylowicz, C.M., Lee, T.H., 2014. Urban particulate matter suppresses priming of T helper type 1 cells by granulocyte/macrophage colony-stimulating factor-activated human dendritic cells. Am. J. Respir. Cell Mol. Biol.

Matthias-Maser, S., Jaenicke, R., 1995. The size distribution of primary biological aerosol particles with radii > 0.2 µm in an urban/rural influenced region. Atmos. Res. 39, 279–286. https://doi.org/10.1016/0169-8095(95)00017-8

Matthias-Maser, S., Obolkin, V., Khodzer, T., Jaenicke, R., 2000. Seasonal variation of primary biological aerosol particles in the remote continental region of Lake Baikal/Siberia. Atmos. Environ. 34, 3805–3811. https://doi.org/10.1016/S1352-2310(00)00139-4

Mbareche, H., Morawska, L., Duchaine, C., 2019. On the interpretation of bioaerosol exposure measurements and impacts on health. J. Air Waste Manag. Assoc. 69, 789–804. https://doi.org/10.1080/10962247.2019.1587552

Menetrez, M.Y., Foarde, K.K., Esch, R.K., Schwartz, T.D., Dean, T.R., Hays, M.D., Cho, S.H., Betancourt, D.A., Moore, S.A., 2009. An evaluation of indoor and outdoor biological particulate matter. Atmos. Environ. 43, 5476–5483. https://doi.org/10.1016/j.atmosenv.2009.07.027

Michael, S., Montag, M., Dott, W., 2013. Pro-inflammatory effects and oxidative stress in lung macrophages and epithelial cells induced by ambient particulate matter. Environ. Pollut. 183, 19–29.

https://doi.org/10.1016/j.envpol.2013.01.026

Mirsaeidi, M., Motahari, H., Khamesi, M.T., Sharifi, A., Campos, M., Schraufnagel, D.E., 2016. Climate change and respiratory infections. Ann. Am. Thorac. Soc. 13, 1223–1230. https://doi.org/10.1513/AnnalsATS.201511-729PS

Mirskaya, E., Agranovski, I.E., 2018. Sources and mechanisms of bioaerosol generation in occupational environments. Crit. Rev. Microbiol. 44, 739–758. https://doi.org/10.1080/1040841X.2018.1508125

Mishra, R., Krishnamoorthy, P., Gangamma, S., Raut, A.A., Kumar, H., 2020. Particulate matter (PM10) enhances RNA virus infection through modulation of innate immune responses. Environ. Pollut. https://doi.org/10.1016/j.envpol.2020.115148

Monks, P.S., Granier, C., Fuzzi, S., Stohl, A., Williams, M.L., Akimoto, H., Amann, M., Baklanov, A., Baltensperger, U., Bey, I., Blake, N., Blake, R.S., Carslaw, K., Cooper, O.R., Dentener, F., Fowler, D., Fragkou, E., Frost, G.J., Generoso, S., Ginoux, P., Grewe, V., Guenther, A., Hansson, H.C., Henne, S., Hjorth, J., Hofzumahaus, A., Huntrieser, H., Isaksen, I.S.A., Jenkin, M.E., Kaiser, J., Kanakidou, M., Klimont, Z., Kulmala, M., Laj, P., Lawrence, M.G., Lee, J.D., Liousse, C., Maione, M., McFiggans, G., Metzger, A., Mieville, A., Moussiopoulos, N., Orlando, J.J., O'Dowd, C.D., Palmer, P.I., Parrish, D.D., Petzold, A., Platt, U., Pöschl, U., Prévôt, A.S.H., Reeves, C.E., Reimann, S., Rudich, Y., Sellegri, K., Steinbrecher, R., Simpson, D., ten Brink, H., Theloke, J., van der Werf, G.R., Vautard, R., Vestreng, V., Vlachokostas, C., von Glasow, R., 2009. Atmospheric composition change – global and regional air quality. Atmos. Environ. 43, 5268–5350. https://doi.org/10.1016/j.atmosenv.2009.08.021

Morawska, L., Cao, J., 2020. Airborne transmission of SARS-CoV-2 : The world should face the reality. Environ. Int. 139, 105730. https://doi.org/10.1016/j.envint.2020.105730

Müller, L., Chehrazi, C.V.E., Henderson, M.W., Noah, T.L., Jaspers, I., 2013. Diesel exhaust particles modify natural killer cell function and cytokine release. Part. Fibre Toxicol. 10, 1–10. https://doi.org/10.1186/1743-8977-10-16

Naeher, L.P., Brauer, M., Lipsett, M., Zelikoff, J.T., Simpson, C.D., Koenig, J.Q., Smith, K.R., 2007. Woodsmoke Health Effects: A Review. Inhal. Toxicol. 19, 67–106. https://doi.org/10.1080/08958370600985875

Nazaroff, W.W., 2016. Indoor bioaerosol dynamics. Indoor Air 26, 61–78. https://doi.org/10.1111/ina.12174

Nemmar, A., Hoylaerts, M.F., Hoet, P.H.M., Nemery, B., 2004. Possible mechanisms of the cardiovascular effects of

inhaled particles: Systemic translocation and prothrombotic effects. Toxicol. Lett. 149, 243–253. https://doi.org/10.1016/j.toxlet.2003.12.061

Ni, L., Chuang, C.C., Zuo, L., 2015. Fine particulate matter in acute exacerbation of COPD. Front. Physiol. 6, 1–10. https://doi.org/10.3389/fphys.2015.00294

Niazi, S., Groth, R., Spann, K., Johnson, G.R., 2020. The role of respiratory droplet physicochemistry in limiting and promoting the airborne transmission of human coronaviruses: A critical review. Environ. Pollut. 115767. https://doi.org/10.1016/j.envpol.2020.115767

Oh, S.M., Kim, H.R., Park, Y.J., Lee, S.Y., Chung, K.H., 2011. Organic extracts of urban air pollution particulate matter (PM2.5)-induced genotoxicity and oxidative stress in human lung bronchial epithelial cells (BEAS-2B cells). Mutat. Res. - Genet. Toxicol. Environ. Mutagen. 723, 142–151. https://doi.org/10.1016/j.mrgentox.2011.04.003

Pant, P., Harrison, R.M., 2013. Estimation of the contribution of road traffic emissions to particulate matter concentrations from field measurements: A review. Atmos. Environ. 77, 78–97. https://doi.org/10.1016/j.atmosenv.2013.04.028

Peixoto, M.S., de Oliveira Galvão, M.F., Batistuzzo de Medeiros, S.R., 2017. Cell death pathways of particulate matter toxicity. Chemosphere 188, 32–48. https://doi.org/10.1016/j.chemosphere.2017.08.076

Piazzalunga, A., Belis, C., Bernardoni, V., Cazzuli, O., Fermo, P., Valli, G., Vecchi, R., 2011. Estimates of wood burning contribution to PM by the marker-tracer method using tailored emission factors. Atmos. Environ. 45, 6642–6649. https://doi.org/10.1016/j.atmosenv.2011.09.008

Pope III, C.A., Burnett, R.T., Thurston, G.D., Thun, M.J., Calle, E.E., Krewski, D., Godleski, J.J., 2004. Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution. Circ. Res. 71–77. https://doi.org/10.1161/01.CIR.0000108927.80044.7F

Pöschl, U., 2005. Atmospheric Aerosols: Composition, Transformation, Climate and Health Effects. Angew. Chemie Int. Ed. 44, 7520–7540. https://doi.org/10.1002/anie.200501122

Putaud, J.P., Van Dingenen, R., Alastuey, A., Bauer, H., Birmili, W., Cyrys, J., Flentje, H., Fuzzi, S., Gehrig, R., Hansson, H.C., Harrison, R.M., Herrmann, H., Hitzenberger, R., Hüglin, C., Jones, A.M., Kasper-Giebl, A., Kiss, G., Kousa, A.,

Kuhlbusch, T.A.J., Löschau, G., Maenhaut, W., Molnar, A., Moreno, T., Pekkanen, J., Perrino, C., Pitz, M., Puxbaum, H., Querol, X., Rodriguez, S., Salma, I., Schwarz, J., Smolik, J., Schneider, J., Spindler, G., ten Brink, H., Tursic, J., Viana, M., Wiedensohler, A., Raes, F., 2010. A European aerosol phenomenology - 3: Physical and chemical characteristics of particulate matter from 60 rural, urban, and kerbside sites across Europe. Atmos. Environ. 44, 1308–1320. https://doi.org/10.1016/j.atmosenv.2009.12.011

Querol, X., Tobías, A., Pérez, N., Karanasiou, A., Amato, F., Stafoggia, M., Pérez García-Pando, C., Ginoux, P., Forastiere, F., Gumy, S., Mudu, P., Alastuey, A., 2019. Monitoring the impact of desert dust outbreaks for air quality for health studies. Environ. Int. 130, 104867. https://doi.org/10.1016/j.envint.2019.05.061

Raes, F., Dingenen, R. Van, Elisabetta, V., Wilson, J., Putaud, J.P., Seinfeld, J.H., Adams, P., 2002. Chapter 18 Formation and cycling of aerosols in the global troposphere. Dev. Environ. Sci. 1, 519–563. https://doi.org/10.1016/S1474-8177(02)80021-3

Ramachandran, S., 2018. Atmospheric Aerosols: Characterist cs and Radiative Effects - 1st Edit. CRC Press.

Ramshaw, I.A., Ramsay, A.J., Karupiah, G., Rolph, M.S., Mahalingam, S., Ruby, J.C., 1997. Cytokines and immunity to viral infections. Immunol. Rev. https://doi.org/10.1111/j.1600-065X.1997.tb01011.x

Rebuli, M.E., Speen, A.M., Martin, E.M., Addo, K.A., Pawlak, E.A., Glista-Baker, E., Robinette, C., Zhou, H., Noah, T.L., Jaspers, I., 2019. Wood smoke exposure alters human inflammatory responses to viral infection in a sex-specific manner: A randomized, placebo-controlled study. Am. J. Respir. Crit. Care Med. 199, 996–1007. https://doi.org/10.1164/rccm.201807-1287OC

Reid, J.S., Koppmann, R., Eck, T.F., Eleuterio, D.P., 2005. A review of biomass burning emissions part II: intensive physical properties of biomass burning particles. Atmos. Chem. Phys. 5, 799–825. https://doi.org/10.5194/acp-5-799-2005

Ren, H., Jin, Y., Hu, M., Zhou, J., Song, T., Huang, Z., Li, B., Li, K., Zhou, W., Dai, H., Shi, W., Yue, J., Liang, L., 2016. Ecological dynamics of influenza A viruses: Cross-species transmission and global migration. Sci. Rep. https://doi.org/10.1038/srep36839

Riffault, V., Arndt, J., Marris, H., Mbengue, S., Setyan, A., Alleman, L.Y., Deboudt, K., Flament, P., Augustin, P., Delbarre, H., Wenger, J., 2015. Fine and Ultrafine Particles in the Vicinity of Industrial Activities: A Review. Crit.

Rev. Environ. Sci. Technol. 45, 2305–2356. https://doi.org/10.1080/10643389.2015.1025636

Rothen-Rutishauser, B., Blank, F., Mühlfeld, C., Gehr, P., 2008. In vitro models of the human epithelial airway barrier to study the toxic potential of particulate matter. Expert Opin. Drug Metab. Toxicol. 4, 1075–1089. https://doi.org/10.1517/17425255.4.8.1075

Rothen-Rutishauser, B., Mühlfeld, C., Blank, F., Musso, C., Gehr, P., 2007. Translocation of particles and inflammatory responses after exposure to fine particles and nanoparticles in an epithelial airway model. Part. Fibre Toxicol. 4, 1–9. https://doi.org/10.1186/1743-8977-4-9

Ruzer, L.S., Harley, N.H., 2012. Aerosols Handbook, Aerosols Handbook: Measurement, Dosimetry, and Health Effects, Second Edition. CRC Press. https://doi.org/10.1201/b12668

Saravia, J., You, D., Thevenot, P., Lee, G.I., Shrestha, B., Lomnicki, S., Cormier, S.A., 2014. Early-life exposure to combustion-derived particulate matter causes pulmonary immunosuppression. Mucosal Immunol. 7, 694–704. https://doi.org/10.1038/mi.2013.88

Sawyer, K., Mundandhara, S., Ghio, A.J., Madden, M.C., 2010. The effects of ambient particulate matter on human alveolar macrophage oxidative and inflammatory responses. J. Toxicol. Environ. Heal. - Part A Curr. Issues 73, 41–57. https://doi.org/10.1080/15287390903248901

Schuit, M., Gardner, S., Wood, S., Bower, K., Williams, G., Freeburger, D., Dabisch, P., 2020. The Influence of Simulated Sunlight on the Inactivation of Influenza Virus in Aerosols. J. Infect. Dis. 221, 372–378. https://doi.org/10.1093/infdis/jiz582

Schwarze, P.E., Øvrevik, J., Låg, M., Refsnes, M., Nafstad, P., Hetland, R.B., Dybing, E., 2006. Particulate matter properties and health effects: Consistency of epidemiological and toxicological studies. Hum. Exp. Toxicol. 25, 559–579. https://doi.org/10.1177/096032706072520

Seinfeld, J.H., Pandis, S.N., 2006. Atmospheric Chemistry and Physics: From Air Pollution to Climate Change - Second Edition. John Wiley and sons.

Shaughnessy, W.J., Venigalla, M.M., Trump, D., 2015. Health effects of ambient levels of respirable particulate matter (PM) on healthy, young-adult population. Atmos. Environ. 123, 102–111.

https://doi.org/10.1016/j.atmosenv.2015.10.039

Shen, F., Zheng, Y., Niu, M., Zhou, F., Wu, Yan, Wang, J., Zhu, Tong, Wu, Yusheng, Wu, Z., Hu, M., Zhu, Tianle, 2019. Characteristics of biological particulate matters at urban and rural sites in the North China Plain. Environ. Pollut. 253, 569–577. https://doi.org/10.1016/j.envpol.2019.07.033

Silverman, M., Povitz, M., Sontrop, J.M., Li, L., Richard, L., Cejic, S., Shariff, S.Z., 2017. Antibiotic prescribing for nonbacterial acute upper respiratory infections in elderly persons. Ann. Intern. Med. 166, 765–774. https://doi.org/10.7326/M16-1131

Soleimani, Z., Teymouri, P., Darvishi Boloorani, A., Mesdaghinia, A., Middleton, N., Griffin, D.W., 2020. An overview of bioaerosol load and health impacts associated with dust storms: A focus on the Middle East. Atmos. Environ. 223, 117187. https://doi.org/10.1016/j.atmosenv.2019.117187

Tang, J.W., 2009. The effect of environmental parameters on the survival of airborne infectious agents. J. R. Soc. Interface 6. https://doi.org/10.1098/rsif.2009.0227.focus

Tomasi, C., Fuzzi, S., Kokhanovsky, A. (Eds.), 2017. Atmospheric Aerosols: Life Cycles and Effects on Air Quality and Climate. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. https://doi.org/10.1002/9783527336449

U.S. EPA, 2019. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, 2019).

Upadhyay, S., Ganguly, K., Stoeger, T., 2014. Inhaled ambient particulate matter and lung health burden. EMJ Respir.

US EPA, 2004. Air Quality Criteria for Particulate Matter, Air Quality Criteria for Particulate Matter.

Van Eeden, S.F., Yeung, A., Quinlam, K., Hogg, J.C., 2005. Systemic response to ambient particulate matter: Relevance to chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. 2, 61–67. https://doi.org/10.1513/pats.200406-035MS

Van Noort, S.P., Aguas, R., Ballesteros, S., Gomes, M.G.M., 2012. The role of weather on the relation between influenza and influenza-like illness. J. Theor. Biol. 298, 131–137. https://doi.org/10.1016/j.jtbi.2011.12.020

Vandini, S., Corvaglia, L., Alessandroni, R., Aquilano, G., Marsico, C., Spinelli, M., Lanari, M., Faldella, G., 2013. Respiratory syncytial virus infection in infants and correlation with meteorological factors and air pollutants. Ital. J. Pediatr. 39, 1–6. https://doi.org/10.1186/1824-7288-39-1

Vecchi, R., Marcazzan, G., Valli, G., 2007. A study on nighttime – daytime PM10 concentration and elemental composition in relation to atmospheric dispersion in the urban area of Milan (Italy). Atmos. Environ. 41, 2136–2144. https://doi.org/10.1016/j.atmosenv.2006.10.069

Whitby, K.T., 1978. The physical characteristics of sulfur aerosols. Atmos. Environ. 12, 135–159. https://doi.org/10.1016/0004-6981(78)90196-8

WHO, 2016. Ambient Air Pollution: A global assessment of exposure and burden of disease. World Heal. Organ.

Wilson, W.E., Chow, J.C., Claiborn, C., Fusheng, W., Engelbrecht, J., Watson, J.G., 2002. Monitoring of particulate matter outdoors. Chemosphere 49, 1009–1043. https://doi.org/10.1016/S0045-6535(02)00270-9

Xia, X., Yao, L., 2019. Spatio-Temporal Differences in Health Effect of Ambient PM2.5 Pollution on Acute Respiratory Infection Between Children and Adults. IEEE Access 7, 25718–25726. https://doi.org/10.1109/ACCESS.2019.2900539

Yang, H.S., Sim, H.J., Cho, H., Bang, W.Y., Kim, H.E., Kwon, T.K., Kwon, T., Park, T.J., 2020. Alpha-tocopherol exerts protective function against the mucotoxicity of particulate matter in amphibian and human goblet cells. Sci. Rep. 10, 6224. https://doi.org/10.1038/s41598-020-63085-6

Yeh, C.F., Lee, C.L., Brimblecombe, P., 2017. Effects of seasonality and transport route on chemical characteristics of PM2.5 and PM2.5-10 in the East Asian pacific rim region. Aerosol Air Qual. Res. https://doi.org/10.4209/aaqr.2016.12.0569

Zelikoff, J.T., Chen, L.C., Cohen, M.D., Fang, K., Gordon, T., Li, Y., Nadziejko, C., Schlesinger, R.B., 2003. Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. Inhal. Toxicol. 15, 131–150. https://doi.org/10.1080/08958370304478

Zhai, Y., Li, X., Wang, T., Wang, B., Li, C., Zeng, G., 2018. A review on airborne microorganisms in particulate matters: Composition, characteristics and influence factors. Environ. Int. 113, 74–90. https://doi.org/10.1016/j.envint.2018.01.007

Zhao, C.N., Xu, Z., Wu, G.C., Mao, Y.M., Liu, L.N., Qian-Wu, Dan, Y.L., Tao, S.S., Zhang, Q., Sam, N.B., Fan, Y.G., Zou, Y.F., Ye, D.Q., Pan, H.F., 2019. Emerging role of air pollution in autoimmune diseases. Autoimmun. Rev. 18, 607–614.

https://doi.org/10.1016/j.autrev.2018.12.010

Zhao, Y., Richardson, B., Takle, E., Chai, L., Schmitt, D., 2019. Airborne transmission may have played a role in the spread of 2015 highly pathogenic avian influenza outbreaks in the United States. Sci. Rep. 9, 1–10. https://doi.org/10.1038/s41598-019-47788-z

Zwozdziak, A., Sówka, I., Willak-Janc, E., Zwozdziak, J., Kwiecińska, K., Balińska-Miśkiewicz, W., 2016a. Influence of PM1 and PM2.5 on lung function parameters in healthy schoolchildren—a panel study. Environ. Sci. Pollut. Res. 23, 23892–23901. https://doi.org/10.1007/s11356-016-7605-1

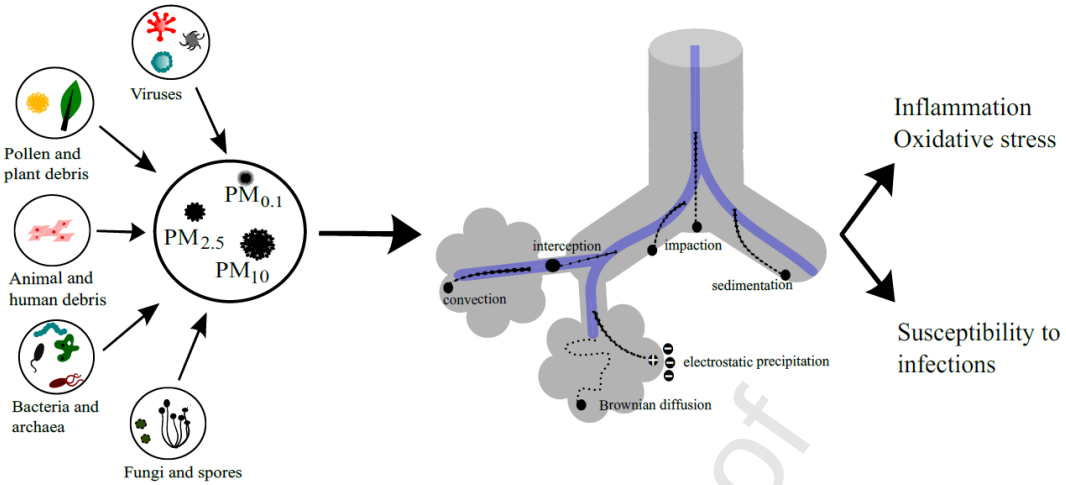
Zwozdziak, A., Sówka, I., Willak-Janc, E., Zwozdziak, J., Kwiecińska, K., Balińska-Miśkiewicz, W., 2016b. Influence of PM1 and PM2.5 on lung function parameters in healthy schoolchildren—a panel study. Environ. Sci. Pollut. Res. 23, 23892–23901. https://doi.org/10.1007/s11356-016-7605-1

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical abstract



Highlights

- Particulate matter action in infectious diseases needs to be analysed in depth
- Literature results on the possible link between outdoor PM and health outcomes are reviewed
- Pulmonary immunological responses following PM exposure are reported
- The role of BioPM as a source of pathogens is outlined