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Environmental Toxicants Inducing COVID-19 Transmission and Lethality Among Adults and Children

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Abstract : COVID-19 was first of all found in China and from there it spread out throughout the world in the first quarter of 2020. On January 30, 2020, World Health Organization treated this as a matter of a Public Health Emergency of international concern. Subsequently on March 11, 2020 it was declared a pandemic. The cause of COVID - 19 disease was a virus named as Severe Acute Respiratory Syndrome Coronavirus type-2 (SARS-CoV-2) which infects the patient by binding to the angiotensin converting enzyme-2 (ACE-2) receptor expressed in several organs including lungs, heart, kidney and intestine. The infection spreads by expulsion of virus from the infected person through their respiratory systems in to the environment as the pathogens penetrate in to the respective host by inhalation. A number of studies conducted by scientists in China, Italy and USA point out the role of increasing level of air pollutants in fast transmission of SARS-CoV-2 and severity of the disease COVID 19. PM_{10} and $PM_{2.5}$ (Particulate Matter**)** play a vital role in spread of virus as they remain in the air for enough time and act as vector or carrier for the virus and may carry the pathogens for long distances and deeper in to the lungs. Besides PM, pesticides, aerosol containing carbon mono oxide, nitrogen oxides, ozone, heavy metals, and organic chemicals induce oxidative stress which can disrupt the function of respiratory epithelial barrier. These pollutants may also induce inflammation and thereby increasing the susceptibility for the virus and lethality among COVID-19 patients.

Occurrence and severity of COVID -19 disease influenced by toxic environment in adults is suggested through epidemiological evidence. There may be various reasons for this such as-reduced innate immunity by pollutants provides the easy way for entry of virus and presence of enough number of ACE-2 receptors on the respiratory surface of adults in comparison to nose of a child. Thus a child is less prone to getting infected by COVID -19 in comparison to the adults.

Recent research studies of COVID-19 observed that the vulnerability of the virus is less among the children in comparison to adult population. This observation is important in the light of the fact that children are generally more vulnerable than adults to the adverse consequences of air pollution. It was suggested that trained innate immunity and increased immune microenvironment due to increased lymphocytes, T and B cells, NK cells protect the children, Universal BCG vaccination and prior infection with other viruses of coronavirus family in children may provide cross protection to SARS-CoV-2.

Key Words: COVID-19, ACE -2 Receptor, SARS-CoV-2, Particulate Matter (PM), Air Pollutants

Introduction

In the present scenario, man-made activities are deteriorating the environment globally. Heavy industrialization is the root cause of increasing environmental pollutants such as airborne particulate matter, industrial chemicals, heavy metals, strong oxidants such as environmentally persistent free radicals (EPFRs), gases (CO, NOX, O_3, CO_2). Use of pesticides in agriculture, add on some organic compounds in environment such as polychlorinated biphenyls (PCBs), dioxins, organochlorines, organophosphates, carbamates etc., which find their way into human beings through food chain. Urbanization leads to habitat destruction of many biota (flora as well as fauna). Live animal trade and intense livestock farming somehow detrimental to ecosystems and contribute to polluting the environment. The present paper is aimed to take note of the current information about how these environmental factors induce the transmission and lethality of COVID-19 among population. The paper is based on the review of studies focused on some cities of Italy, China & USA. Coronavirus disease *2019* (COVID-19) is the disease targeting directly

respiratory system.

Causal organism is a 'virus named as Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2), as classified by coronovirus study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTU)' (Yu *et al.,* 2020).

On March 11, 2020 the epidemic of SARS-CoV-2 infection was declared as a pandemic due to its fast transmission globally (Gautret *et al.,* 2020). This was first wave of COVID-19, which was followed by second wave in March 2021.

SARS-CoV-2 particles are spherical having spike proteins projecting from their surface (Melanthota *et al.,* 2020). The virus has high affinity for the receptors found on human respiratory surface (Zhang *et al.*, 2020). These receptors (angiotensin-converting Enzyme 2 ACE 2) fuse with spikes present on the surface of the SARS-CoV-2virus; following structural changes in the virus (Xu *et al*., 2020).Viral structural proteins assemble at the host cell membrane to form mature viral progeny, which are released through the secretary vesicles via exocytosis (Li *et al.,* 2019) & ready to infect surrounding cells. This is the way the virus SARS-CoV-2 gets its entry into human alveolar cells or human respiratory system (Xiu *et al*., 2020).

Other sites of SARS-CoV-2 infection include body organs with ACE-2 receptors, which are lower respiratory tract, heart, liver, intestinal tract and kidney (Chioechetti *et al.,* 2020; Dhama *et al.,* 2020).

Airborne Transmission of SARS-CoV-1 and SARS-CoV-2

Expulsion of virus from infected person through their respiratory system into environment from there the pathogens penetrate in to the receptive host by inhalation.

It may spread mainly by three routes: (1) 21% by aerosol, which is a suspension of solid or liquid particles within a gas phase (long distance), (2) 29% by close contact among individuals by droplets or saliva and (3) 50% by contact with surfaces (formite route) (Lie *et al.* 2018). Air pollutants make suitable environment for transmission of virus at greater distances and also could increase susceptibility and severity of COVID-19 patient symptoms.

Particulate matter (PM) and Viral Transmission

Presence of gases such as carbon mono oxide (CO), Nitrogen oxides (NOX), Ozone (O_3) Volatile organic compounds (VOCs), gaseous forms of metals along with contaminating particles or Particulate matter (PM) in the atmosphere are main pollutants affecting SARS CoV-2.

The term 'Particulate matter' (PM) as defined by Environmental Protection Agency (EPA 2021), indicates the set of particles dispersed in the air. (Particulate matter (PM) is mixture of Sulphates, Nitrates, Elemental Carbon, Organic Carbon and Crustal Material). They remain in the air for enough time and may be diffused & transported for long distances. PM is classified as PM 10 and PM 2.5 based on a diameter of less than 10 micrometers and 2.5 micrometers, respectively.Wild fire is main source of their emission. In Lombardy (North of Italy), diesel combustion and solid biomass burning are responsible for 15% and 50% of their production respectively (Naeher *et al.,* 2007).

PM can adsorb other substances such as hydrocarbons, heavy metals thus increasing their toxicity (Mantecca *et al.*, 2012). Metals supposed to accumulate on PM are Mercury (Hg), Chromium (Cr), Cadmium (Cd), Arsenic (As), Lead (Pb) and Uranium. (*Kim et al.,* 2015).

Owing to their small size they are inhalable corpuscles thus affecting respiratory and cardio vascular system (Cassee *et al.,* 2011).

Particulate matter (PM) present in environment act as a transport vector or carrier for virus and along with toxicants. First, PM design a *micro environment* suitable for persistence of virus, thus, increasing spread of virus in the aerosol (Setti *et al.,* 2020).

Micro-organisms and other polluting particles adsorbed by PM also get their entry into host. Inhalation transports the particles deep into the lungs, especially those smaller than 2.5 microns (PM 2.5 and ultrafine particles UFPs) and this allows the entry of virus in to respiratory tract and infect the host. Italian Society of Environmental Medicine (SIMA) considers PM as an important carrier associated with the spread of COVID-19 (Setti *et al.,* 2020). To observe and analyze the effect of increasing level of air pollution on rapid increase in COVID-19's contagion and role of PM in the spread of virus, several studies in different parts of world have been carried out. Three world areas with high number of COVID-19 infected people were found: China, from where pandemic started, Italy and the USA, all having very high level of air pollutants. For this reason, this review is focused on these areas to find a possible correlation in air pollution and COVID -19's contagion.

This possible correlation should be investigated at two levels (A) Long Term Exposition - when high level of air pollution made the population more

sensitive to COVID-19. (B) Short term exposition – Which was to test sensitivity of virus in the condition of high level of air pollution during the period when virus appeared.

During studies on COVID-19 transmission, it was found that long term or Chronic exposure to atmospheric particles (PM), increased hospitalization, mortality, damage in Cardio vascular and respiratory system among COVID-19 patients. (Kampa and Castanas, 2008). In Beijing (China) organisms exposed to air pollutants were tested in a metagenomics analysis for a period of high smog level. The presence of viral particles (0.1% in both PM 10 and PM 2.5) were observed. It was found that quantity of pathogens in respiratory tract is directly proportional to concentration of pollutants (Cao *et al.,* 2014).

Occurrence and severity of COVID-19, due to PM was observed in several areas of USA, exposed to higher levels of air pollution. It was found that higher incidence and mortality rates from PM 2.5 were associated with an 8% increase in risk of death (Wu *et al*., 2020).

Pansini and Fornacca (2020) investigated the geographical expansion of infection & correlated it with the annual indexes of air quality. They observed from Sentinel -5 Satellite orbiting around China, Italy and the USA different pollutants in the atmosphere (PM_{10}, $PM_{2.5}$, Carbon mono oxide, Nitrogen Dioxide and Ozone) & concluded a positive correlation between COVID -19 infections and air quality variables. Higher mortality was reported with $PM_{2.5}$, Carbon mono oxide and Nitrogen dioxide values.

In case of Italy, Fattorini and Regoli (2021) and Contccini *et al.* (2020) also found the similar results.

Above authors concluded that long term exposure of air pollutants increased the severity of COVID-19 in up to 71 Italian provinces, providing further evidence that long-term exposure to air pollution became a mean for the spread of virus.

Pansini and Fornacca (2021) associating several annual satellite and ground indexes of Air quality in China, Iran, Italy, Spain, France, Germany, United Kingdom & USA with COVID-19 infection, suggested a positive correlation between high level of pollutants in the atmosphere and COVID-19 infection.

$PM_{2.5}$ exposure significantly increases lethality in COVID-19 patients (Wu *et al.,* 2020).

Po Valley, the foremost place of polluted air in Europe and in Lombardy high concentration of PM was reported before the COVID-19 pandemic. (ESA, 2020).

Air quality in Italy and China was analyzed by Frontera *et al.* (2020) and $PM_{2.5}$ & Nitrogen dioxide levels were found particularly high. Martelletti and Martelletti (2020) also confirmed the results. Accelerated COVID-19 spread was suggested along with high frequency of PM_{10} (exceeding 50 $\mu g/m^3$) by Setti *et al.* (2020). Zhu *et al.* (2020) reported high value of six daily measured air pollutants (PM_{10}, $PM_{2.5}$, SO_2, CO, NO_2, O_3) associated with COVID-19 positive cases in 120 cities in China between 23 Jan 2020 and 9 Feb 2020 (Short term exposition).

Coccia (2020) reported, more than 75% of infected individuals and about 81% of deaths of first wave of COVID-19 pandemic in Italy were in industrialized region with high levels of air pollution. These were results from February to August 2020.

Role of O_3, CO, NO_2 in transmission of SARS-CoV-2

Several authors reported a relationship between Ozone (O_3) and Nitrogen dioxide (NO_x) and COVID-19. Ozone was importantly found correlated in flagging SARS-CoV-2 transmission (Loli and Vivone, 2020). Main source of CO, NO_2 is crop residue burning.

$1 g/m^3$ Carbon mono-oxide present in atmosphere was found to be responsible for 15.11% increase in the daily count of confirmed COVID-19 cases (Zhu *et al.,* 2020).

Wood Smoke, a source for Carbon monoxide suppresses respiratory immunity even on inhalation at a relatively low level, which results increased susceptibility to viral infections as well as several types of lung diseases (Sarigiannis *et al.,* 2015). This is of particular importance in case of SARS-CoV-2 infection as the target organ in this case is respiratory system.

COVID-19 transmissions accelerated with increase of CO (Carbon mono-oxide), NO_2 (Nitrogen Oxide) and O_3 (Ozone) levels in the atmosphere (Zhu *et al.,* 2020).

In Italy, Spain, France and Germany increased mortality due to COVID-19 was reported on long term exposure to NO_2 (Nitrogen Oxide) by Ogen (2020).

Positive correlation between Nitrogen Dioxide and COVID-19 was reported by Frontera *et al.* (2020) and by Martelletti and Martelletti (2020) in Italy and China.

Correlation of Pesticides, other organic chemicals and heavy metals with SARS-CoV-2 infection

Organophosphorus insecticides are absorbed by skin as well as by respiratory and gastrointestinal tract. They act via a common mechanism of disrupting negative feedback control of cholinergic regulation in lungs, thus promoting neurogenic inflammation in lungs. Synergism with allergen sensitization has also been reported, particularly with fungicides exposure (Hermandez *et al.*, 2011). Pollution induced inflammation resulting in more severe COVID-disease (Menendez, 2020).

Organochlorine, Organophosphates, Carbamates and several other herbicides exert immunotoxic effect. These pesticides can induce release of pro-inflammatory mediators from macrophages thereby inducing oxidative stress.

Oxidative stress impairs respiratory epithelial barrier function (Benmarhnia, 2020) and induces a microenvironment in lungs which is immune suppressive (Lee *et al.*, 2014; Saravia *et al.*, 2014; Sussan *et al.*, 2015; Jaligama *et al.*, 2017) resulting more severe COVID disease (Menendez , 2020).

Heavy metals (particularly Lead) are also immunotoxic substance which can impair immune system and there may be higher risk of inflammatory disorders; increasing incidence of infectious disease, autoimmunity and cancer (Bornstein *et al.*, 2020).

Other toxic metals Cadmium (Cd) and Mercury (Hg) have been reported to decrease immune responses and to increase the risk of infectious disease (Bulka *et al.*, 2020; Emeny *et al*., 2019; Prins *et al.,* 2009).

Organic Compounds polychlorinated biphenyls *(PCBs),* dioxins and polyfluoro alkyl substances *(PFAS)* also play an important role in suppressing the immune system (Costa *et al.,* 2013; Diamanti-Kandarakis *et al*., 2009; Fenga *et al*., 2014; Gascon *et al*., 2012; Mokarizadeh *et al.,* 2015).

On their exposure risk of lower respiratory tract infection and other infections later in childhood are increased (Goudarzi *et al.,* 2017; Granum *et al.,* 2013; Impenen *et al*., 2017) while exposure to PCBs and dioxins increase upper respiratory tract infection during infancy (Stolevik *et al.,* 2013).

These exposures to immunotoxic substances reduce anti-viral innate immune responses may could increase the risk of COVID-19.

SARS CoV-2 Infection among the Children

Peter D. Sly *et al.* (2021) reported in their study occurrence of the disease COVID-19 among the children.

> 32% in children (Age group between 15-17 years)

> 27% in children (Age group between 10-14 years)

> 15% in children (Aged < 1 years)

> 11% in children (Age between 1-4 years)

> 15% in children (Age between 5-9 years)

(Source: MMWRMorb Mortal Wkly Rpt. 2020)

This observation is important in the light of the fact that children are generally more vulnerable than adults to the adverse consequences of air pollution.

It suggests that there may be different modes to explain the interaction between SARS CoV-2 infection and air pollution in children and in adults. Immune system of children seems efficient to eliminate virus than adults. Children have a strong innate immune response from birth having intrinsic elevation of lymphocytes, including T, B and NK cells. (Cristiani *et al.,* 2020). A Strong immune microenvironment in their lungs as their T-cells are relatively native and untrained, having a greater capacity to respond to new viruses, thereby preventing a strong immune and inflammatory response in the lungs; may protect children from severe disease (Muyayalo *et al.*, 2020).

Children are usually main reservoir for seasonal corona viruses & bacteria (Lambert, 2012).

This prior infections may provide cross protection to SARS-CoV-2.

Nose of Child contain fewer ACE-2 receptors (the binding site of SARS CoV-2) so they are less prone to infection (Tosif *et al.,* 2020).

Conclusion

Atmosphere rich in air pollutants such as air borne particulate matter, gases, namely, Carbon monoxide (CO), Nitrogen oxide (NO_2), Ozone (O_3), industrial chemicals, heavy metals, pesticides and some other toxic organic chemicals play a vital role in the transmission of SARS CoV-2 & severity of disease COVID-19, directly or indirectly (Frontera *et al.* 2020).

As respiratory surface is the first target of Particulate Matter (PM), two mechanisms have been demonstrated to be induced in lungs after PM exposure, both in humans & experimental models (Mantecca *et al*., 2009): 1) Oxidative stress: - Production of free radicals that induce damage of cells; and 2) Inflammation: - PM induces activation of immune response and thus cell enters in an inflammatory state. This cellular condition facilitates the attack of viruses and increases the severity of COVID-19 patients.

PM may have played a carrier role for COVID-19 as they remain in air for enough time and can adsorb other toxicants, thereby causing lethality in COVID-19 patients.

This hypothesis could explain the positive correlation between COVID-19, the PM concentration and high mortality rate in polluted areas.

Oxidative stress induced by other air pollutants can impair respiratory epithelial barrier function, reduce innate immune antiviral responses, impair macrophage function resulting in more severe COVID disease (Menendez *et al.*, 2020), $PM_{2.5}$ being smaller size particles may carry SARS-CoV-2 deeper into the lungs (Comunian *et al.,* 2020). Innate immune responses are modified by air pollutants initiated via toll-like receptors (Bauer *et al.*, 2012).

In children, however, severity of COVID-19 disease in polluted environment was not found as among adults. It was suggested that due to strong innate immunity, prior infection with coronavirus family made them less prone to COVID-19 disease.

SARS CoV-2 binds to the angiotensin converting Enzyme 2 (ACE 2) receptors, present on the surface of lungs, arteries, heart, kidney and intestine cells. It regulates blood pressure by catalyzing the cut of the *vasoconstrictor peptide:* angiotensin2, into angiotensin 1-7, which is a *vasodilator* and *anti-inflammatory molecule*. (Hayashi *et al*., 2020).

As blood pressure (BP) increases with age, so to compensate or regulate the BP body expresses a greater number of ACE 2 on cell membranes, thereby providing more receptive sites for SARS-CoV-2. But the nose of a child has less number of ACE 2 receptors which make them less prone to virus.

When ACE 2 is over-expressed following exposure to $PM_{2.5}$, it could increase probability of COVID-19 infection, as ACE 2 is the entry key for the virus.

All above mentioned studies conclude that both long-term & short-term exposure to high levels of pollutants suppress immune system or protection mechanism of our body. In this way, immunotoxic elements are correlated to increase in occurrence of COVID-19 disease & its severity worldwide. New research findings show that environmental toxicants make the habitat within human ecosystem favourable for pathogens.

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References

Bauer R.N. Diaz-Sanchez D. and Jaspers I. (2012). Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-bindingoligomerization domain-like receptors. J. Allergy Clin Immunol.;129(1):14–26.

Benmarhnia T. (2020). Linkages between air pollutionand the health burden from COVID-19:methodological challenges and opportunities.Am J Epidemiol.;189(11):1238–43.

Bornstein S.R. Voit-Bak K. Schmidt D. Morawietz H. Bornstein A.B. Balanzew W. Julius U. Rodionov R.N. Biener A.M. Wang J. Schulte K.M. Krebs P. Vollmer G. and Straube R. (2020). Is there a role for environmental and metabolicfactors predisposing to severe COVID-19.HormMetab Res.; July,52(7):540–6.(doi.org/10.1055/a-1182-2016).

Bulka C.M. Bommarito P.A. Aiello A.E. and Fry R.C. (2020). Cytomegalo virus sero prevalence, recurrence, and antibodylevels: Associations with cadmium and leadexposures in the general United Statespopulation. Environmental epidemiology (Philadelphia, Pa.).;4(4):e100.

Cao C. Jiang W. Wang B. Fang J. Lang J. Tian G. Jiang J. and 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.

Cassee F.R. Mills N.L. and Newby D.E. (2011). Cardiovascular Effects of Inhaled Ultrafine and Nano sized particles. New York: John Wiley & Sons.

Chioechetti R. Galiazzo G. Fracassi F. Giancola F. and Pietra M. (2020). ACE2 Expressions in the Cat and the tiger gastrointestinal tar acts. Front Vet Sci.;7: 514.

Coccia M. (2020). Factors determining the diffusion of COVID-19 and suggested strategy to prevent future accelerated virus infectivity similar to COVID. Sci Total Environ.; 729: 138474.120.

Comunian S. Dongo D. Milani C. and Palestini P. (2020). Air pollution and Covid-19: the role of particulate matter in the spread and increase of Covid-19's morbidity and mortality. Int J Environ Res Public Health.; 17(12):4487.

Contccini E. Frediani B. and Caro D. (2020). Can atmospheric pollution be considered a co-factor in extremely high level of Sars-CoV-2 lethality in Northern Italy? Environ Pollut.; (doi:10.1016/jenvpol.2020.114465)

Costa C. Rapisarda V. Catania S. Nola C.D. Ledda C. and Fenga C. (2013). Cytokine patterns ingreen house workers occupationally exposed toa-cypermethrin: an observational study. Environ Toxicol Pharmacol.;36(3):796800.

(doi.org/10.1016/j.etap.2013.07.004).

Cristiani L. Mancino E. Matera L. Nenna R. Pierangeli A. Scagnolari C. and Midulla F. (2020).Willchildren reveal their secret? The coronavirusdilemma. Eur Respir J.; 55(4):2000749. (doi.org/10.1183/13993003.00749-2020).

Dhama K. Patel S.K. Pathak M. Yatoo M.I. Tiwari R. Malik Y.S. Singh R. Sah R. Ali A. Rabaan A.A. Bonilla-Aldana D.K. and Rodriguez-Morales A.J. (2020). An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. Travel Med Infect Dis.; 37:101755. (doi: 10.1016/j.tmaid.2020.101755).

Diamanti-Kandarakis E. Bourguignon J.P. Giudice L.C. Hauser R. Prins G.S. Soto A.M. Zoeller R.T. and Gore A.C. (2009). Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev.; 30(4): 293–342. (doi.org/10.1210/er.2009-0002).

Emeny R.T. Korrick S.A. Li Z. Nadeau K. Madan J. Jackson B. Baker E. and Karagas M.R. (2019). Prenatalexposure to mercury in relation to infantinfections and respiratory symptoms in the New Hampshire birth cohort study. Environ Res.; 171:523–9. (doi.org/10.1016/j.envres.2019.01.026).

EPA (2021). Particulate Matter (PM) Pollution. https://www.epa.gov/pm-Pollution/particulate-matter-pm-basics#PM. [accessed Jan 21 2022].

ESA (2020). Coronavirus Lockdown leading to Drop in Pollution across Europe. ESA / Applications / Observing the Earth / Copernicus / Sentinel-5P.https://www.era.int/ Applications/ observing_the_earth/copernicus/ sentine15p/coronavirus_lockdown_leading_to_drop_in_pollution_across_Europ. [accessed Jan 21 2022].

Fattorini D. and Regoli F. (2020). Role of the chronic, air pollution levels in the COVID-19 outbreak risk in Italy. Environ. Pollut.; 264:114732. (doi: 10.1016/j.envpol.2020.114732). https://pubmed.ncbi.nlm.nih.gov/32387671/ [accessed Jan 21 2022].

Fenga C. Gangemi S. Catania S. de-Luca A. and Costa C. (2014). IL-17 and IL-22 serum levels in greenhouse workers exposed to pesticides. Inflamm Res.; 63(11):895–7. (doi.org/10.1007/s00011-014-0769-6).

Frontera A. Marlin C. Viachos K. and Sgubin G. (2020). Regional air pollution persistence links to COVID-19 infection zoning. J. Infect.; (doi: 10.1016/j.jinf.2020.03.045).https://pubmed.ncbi.nlm.nih.gov/32283151/ [accessed Jan 21 2022].

Gascon M. Morales E. Sunyer J. and Vrijheid M. (2012). Effects of persistent organic pollutants on the developing respiratory and immune systems: a systematic review. Environ Int.; 52:51–65. (doi.org/10.1016/j.envint.2012.11.005).

Gautrct P. Lagier J. C. Parola P. Hoang, V.T. Meddeb L. Mailhe M. Doudier B. Courjon J. Giordanengo V. Vieira V.E. Dupont H.T. Honoré S. Colson P. Chabrière E. La-Scola B. Rolain J.M., Brouqui P. and Raoult D. (2020). Hydroxychloroq-uine and azithromycin as a treatment of COVID-19: results of anopen-label non-randomized clinical trial, Int J Antimicrobe Agents.; 56:105949.

Goudarzi H. Miyashita C. Okada E. Kashino I. Chen C.J. I to S. Araki A. Kobayashi S. Matsuura H. and Kishi R. (2017). Prenatal exposure toperfluoroalkyl acids and prevalence ofinfectious diseases up to 4years of age. EnvironInt.; 104:132–8.

Granum B. Haug L.S. Namork E.Stølevik S.B. Thomsen C. Aaberge I.S. Loveren H.V. Løvik M. and Nygaard U.C. (2013). Pre-natal exposure to perfluoro alkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. J Immunotoxicol.; 10 (4):373–9.

Hayashi N. Yamamoto K. Ohishi M. Tatara Y. Takeya Y. Shiota A. Oguro R. Iwamoto Y. Takeda M. and Rakugi H. (2010). The counter regulating role of ACE2 and ACE2- mediated angiotensin 1-7 signaling against angiotensin II stimulation in vascular cells. Hypertens Res.; 33:1192-1185. (doi: 10.1038/hr.2010.147).

Hernández, A.F. Parrón T. and Alarcón R. (2011). Pesticides and asthma. Curr Opin Allergy ClinImmunol.; 11(2): 90-6. (DOI: 10.1097/ACI.0b013e3283445939).

Impinen A. Nygaard U.C. Lødrup-Carlsen K.C. Mowinckel P. Carlsen K.H.Haug L.S.and Granum B. (2017). Prenatal exposure to perfluoralkyl substances (PFASs) associated with respiratory tract infections but not allergy and asthma-related health outcomes in childhood. Environmental Research.; 160: 518-523.

Jaligama S. Saravia J. You D. Yadav N. Lee G.I.Shrestha B.and Cormier S.A. (2017). Regulatory T cells andIL10 suppress pulmonary host defense during early-life exposure to radical containing combustion derived ultrafine particulate matter. Respir Res.;18(1):15.

Kampa M. and Castanas E. (2008). Human health effects of air pollution, Environ Pollut.; 151:362-367. (doe: 10.1016/j.envpol.2007.06.012).www.elsevier.com/locate/envpol[accessed Jan 22 2022].

Kim K.H. Kabir E. and Kabir S. (2015). A review on the human health impact of airborne particulate matter. Environ. Int.; 74:136-143.

Lambert S.B. Ware R.S. Cook A.L. Maguire F.A. Whiley D.M. Bialasiewicz S. Ian M. Mackay I.M., Wang D.

Sloots T.P. Nissen M.D. and Grimwood K. (2012). Observational Research in Childhood Infectious Diseases (ORChID): adynamic birth cohort study. BMJ Open.; 2(6): e002134. (doi: 10.1136/bmjopen-2012-002134).

Lee G.I. Saravia J. You D. Shrestha B. Jaligama S. Hebert V.Y. Dugas T.R. and Cormier S.A. (2014). Exposure to combustion generatedenvironmentally persistent free radicalsenhances severity of influenza virus infection.Part Fibre Toxicol.; 11:57.

Lei H. Li Y. Xiao S. Lin C.H. Norris S.L. Wei D. Hu Z. and Ji S. (2018). Routes of transmission of influenza A HIN 1, SARSCoV, and norovirus in air cabin: Comparative analyses. In door Air.; 28:394-403. .

Li Y.H. Hu C.Y. Wu N.P. Vao H.P. Li L.J. (2019). Molecular characteristics, functions and related pathogenicity of MERS-CoV proteins. Engineering (Beijing); 5:940-947.

Lolli S. and Vivone G. (2020). The role of tropospheric ozone in flagging COVID-19 pandemic transmission. Bull Atmos. Sci. Technol.; 1:551 – 5.

Mantecca P. Sancini G. Moschini F. Farina F. Gualtieri M. Robr A. Miserocchi G. Palestini P. and Camatini M. (2009). Lung toxicity induced by intra tracheal instillation of size-fractionated tire particles; Toxicol. Lett.; 89(3):206-14.

Mantecca P. Gualtieri M. Longhin E. Bestetle G. Palestini P. Bolzacchini E. and Camatini M. (2012). Adverse biological effects of Milan urban PM looking for suitable molecular markers of exposure. Chem. Ind. Chem. Eng. Q.; 18:635-641.

Martelletti L. and Martelletti (2020). P. Air Pollution and the Novel COVID-19 Disease: A Putative Disease Risk Factor. SN Compr. Clin. Med.; 2:1-5.

Melanthota S.K. Sanik S. Chakraborty I. Pallen S. Gopal D. Chakrabarti S. and Maazumdar N. (2020) Elucidating the microscopic and computational techniques to study the structure and pathology of SARS-CoVs. Microse Res Tch.; 83:1623-1638.

Menendez J.A. (2020). Metformin and SARS-CoV-2: mechanistic lessons on air pollution to weather the cytokine/thrombotic storm in COVID-19.Aging (Albany NY).; 12(10):8760–5.

MMWR Morb Mortal Wkly Rpt. (2020). CoronaviruseDisease 2019 in Children - United States, Feb12- April 2. https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm[accessed May 22 2021].

Mokarizadeh A. Faryabi M.R. Rezvanfar M.A.and Abdollahi M. (2015). A comprehensive review of pesticides and the immune dysregulation: mechanisms, evidence and consequences. Toxicol Mech Methods.; 25(4):258–78.

Muyayalo K.P. Huang D. Zhao S. Xie T. Mor G. and Liao A. (2020). COVID-19 and Treg/Th17imbalance: Potential relationship to pregnancy outcomes. Am J Reprod Immunol.; e13304.(doi: 10.1111/aji.13304) https://pubmed.ncbi.nlm.nih.gov/32662111/[accessed May 22 2021].

Naeher L.P. Brauer M. Lipsett M. Zelikoff J.T. Simpson C.D. Koenig J.Q. and Smith K.R. (2007). Wood smoke health effects: A review. Inhale. Toxicol.; 19(1) :67-106.

Ogen Y. (2020). Assessing nitrogen dioxide. (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. Sci Total Environ.; 126:138605. (doi.org/10.1016/j.scitotenv.2020.138605) https://www.sciencedirect.com/science/article/pii/S0048969720321215?via%3Dihub(accessed May 22 2021].

Pansini R. and Fornacca D. (2020). Initial evidence of higher morbidity and mortality due to SARS-CoV-2 in regions with lower air quality. Med R.; XIV https://www.medrxiv.org/content/10.1101/2020.04.04.20053595v2. [accessed May 22 2021].

Pansini R. and Fornacca D. (2021). Higher virulence of COVID-19 in the Air-Polluted Regions of Eight Severely Affected countries. Med R. XIV. Atmosphere.; 12(6), 795.

Saravia J. You D. Thevenot P. Lee G.I. Shrestha B Lomnicki S. and Cormier S.A. (2014). Early-life exposure to combustion-derived particulate matter causes pulmonary immunosuppression. Mucosal Immunol.; 7(3): 694–704.

Sarigiannis D.A. mKarakitsios S.P. and Kermenidou MV.(2015). Health impact and monetary cost of exposure to particulate matter emitted from biomass burning in large cities. Science of the Total Environment.; 524-525: 319-330.

Setti L. Passarini F. De-Gennaro G. Di-Gilio A. Palmisani J. Buono P. Fornari G. Perrone M. G. Piazzalunga A. and Barbieri P. (2020). Evaluation of the Potential Relationship between Particulate Matters (PM) Pollution and COVID-19 infection spread in Italy. (doi.org/10.1101/2020.04.11.20061713).https://www.medrxiv.org/content/10.1101/2020.04.11.20061713v1[accessed May 22 2021].

Sly P.D. Trottier B.A. Bulka C.M. Cormier C.A. Fobil J. Fry R.C. Kim K.W. KleebergerS. Kumar P. Landrigan P.J. Carlsen K.C.L Pascale A. Polack F. Ruchirawat M. Zar H.J. and Suk W.A. (2021). The interplay between environmental exposures and COVID-19 risks in the health of children Environ Health.; 20(1):34.

Stølevik S.B. Nygaard U.C. Namork E. Haugen M. Meltzer H.M. Alexander J. Knutsen H.K. Aaberge I. Vainio K Loveren HvLøvik M. and Granum B. (2013). Prenatal exposure topolychlorinated biphenyls and dioxins from the maternal diet may be

associated with immune suppressive effects that persist into early childhood. Food Chem Toxicol.;51:165–72.

Sussan T.E. Gajghate S. Thimmulappa R.K. MaJ. Kim J.H. Sudini K. Consolini N. Cormier S.A. Lomnicki S. Hasan F. Pekosz A. and Biswal S. (2015). Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. Plos One.;10(2):e0116861. (doi.org/10.1371/journal.pone.0116861).

Tosif S. Neeland M.R. and Crawford N.W. (2020). Immune responses to SARS-CoV-2 in three children of parents with symptomatic COVID-19. Nat. Commun.; 11, 5703. https://www.nature.com/articles/s41467-020-19545-8.

Wu X. Nethery R.C. Sabath M.B. Braun D. and Dominici F. (2021).Exposure to Air Pollution and COVID-19 Mortality in the United States. Science advances,; 6(45), p.eabd4049. https://projects.iq.harvard.edu/covid-pm. [accessed May 22 2021].

Wu, X., Nethery R.C. Sabath B.M. Braun D. and DominicF. (2020). Exposure to air pollution and COVID-19 mortality in the United States; A nationwide cross-sectional study. MedRxiv.; (doi: 10.1101/2020.04.05.20054502). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7277007/

Xiu S. Dick A. Ju H. Mirzaie S. Abdi F. Cocklin S. Zhan P.and Liu X. (2020). Inhibitors of SARS-CoV-2 entry: current and future opportunities. J. Med Chem.; 63:12256-12274. (doi.org/10.1021/acs.jmedchem.0c00502)https://pubmed.ncbi.nlm.nih.gov/32539378/[accessed May 22 2021].

Xu X. Chen P. Wang J. Feng J. Zhou H. Li X. Zhon W. and Hao P. (2020). Evolution of the novel coronavirus form the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci.; 63(3):457-460. (doi.org/10.107/s11427-020-1637-5). https://pubmed.ncbi.nlm.nih.gov/32009228/[accessed May 22 2021].

Yu J. Chai P. Ge S. and Fan X. (2020). Recent understanding toward coronavirus disease 2019 (Covid – 19): from bench to bedside. Front Cell Dev Biol.; 8: 476. (doi.org/10.3389/fcell.2020.00476) https://www.frontiersin.org/articles/10.3389/fcell.2020.00476/full[accessed May 22 2021].

Zhang H. Zhou P. Wei Y. Yue H. Wang Y. Hu M. Zhang S. Cao T. Yang C. Li M. Guo G. Chen X. Chen Y. Lei M. Liu H. Zhao J. Peng P. and Wang C.Y.R. (2020). Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med.; 172(9):629-632. (doi.org/10.7326/m20-0533). https://pubmed.ncbi.nlm.nih.gov/32163542/[accessed May 22 2021].

Zhu Y. Xie J. Huang F. and Cao L. (2020). Association between short term exposure to air pollution and COVID-19 injection: Evidence from China. Sci. Total Environ.; 727:138704. (doi: 10.1016/J. sci to tenv. 2020.138704). https://www.sciencedirect.com/science/article/pii/S004896972032221X[accessed May 22 2021].