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Exposure To Organic Solvents in Covid-19 Time: A Possible Vulnerability

Guzmán DC[1], Brizuela NO[1], Herrera MO[2], Mejía GB[2], Peraza AV[1], Soto MP[3] and Olguín HJ[*3]

[1]Laboratory of Neuroscience, Instituto Nacional de Pediatria (INP). Mexico City
[2]Laboratory of Experimental Bacteriology, INP, Mexico City
[3]Laboratory of Pharmacology, INP and Dept of Pharmacology, Faculty of Medicine, Universidad Nacional Autónoma de Mexico

***Corresponding author:** Olguin HJ, Pharmacology Laboratory, National Institute of Pediatrics, Mexico City, Mexico. Tel: 5255 5585 7644, E-mail: juarezol@yahoo.com

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Abstract

It is very important to identify and control risk factors of Covid-19 in susceptible subjects for successful treatment and prevention. Both voluntary and involuntary toxic solvent inhalations are becoming an increasing concern in the Covid-19 pandemic, with possible interactions of toxic solvents exposure and covid-19 drugs treatment or synergic effects on oxidative damage parameters within tissues of young or adults vulnerable. These toxic chemicals induce oxidative stress in the skin and other tissues as well as DNA damage, inflammation, skin barrier dysfunction and immune dysregulation; thus, increasing the sensibility of this population.

Key Words: Addiction, Covid-19, Thinner, Antiviral, Ivermectine, Gasoline station attendants

Introduction

Children are highly susceptible to environmental contaminants as their physiology and some metabolic pathways differ from those of adults. Street children, working at busy intersections, are significantly exposed to chemical solvents that are associated with oxidative stress [1].

According to the National Addiction Survey, both voluntary inhalation of industrial solvents and involuntary exposure to them have increased in an important form [2]. In a study conducted by Chiara et al. [3] on occupational exposure to the vapor of common organic solvents showed that all individuals are exposed to certain chemical, physical, biological and environmental organic solvents. The author found methylhyppuric acids (MHIPPs, xylenes metabolite), phenylglyoxylic and mandelic acid (PGA, MA ethylbenzene metabolites) as well as S-benzylmercapturic acid (SBMA, toluene metabolite) in the urine of workers, such as painters in shipyard industry, gasoline station workers etc.

Likewise, Renata et al. [4] found S-Phenylmercapturic acid (SPMA, benzene metabolite) in the urine of subjects working in these areas, while Rizk et al. [5] reported lower levels of antioxidant enzyme activities and trace metals in his study.

On the other hand, volatile organic compounds (VOCs), such as cyclohexane, toluene, acetaldehyde, formaldehyde and acetone, have potentially harmful effects on the skin.

Evidence suggests that proteasome; a major intracellular proteolytic system involved in a broad array of processes such as cell cycle, apoptosis, transcription, DNA repair, protein quality control and antigen presentation; is a VOC target. Proteasome inactivation after VOC exposure is accompanied by apoptosis, DNA damage and protein oxidation. Low protease, which degrades oxidized, dysfunctional and misfolded proteins in the mitochondria, is also a VOC target [6]. Higher incidence of cancer is suspected in subjects exposed to organic solvents. These solvents are characterized by reactive metabolic intermediates that induce oxidative damage on liver, kidney and hematopoietic system [7,8].

Solvent Toxicity

The adverse effects of certain toxicant solvents, such as benzene; toluene, which directly affect hormonal impairments; molecular alterations; oxidative stress and DNA methylation have been reported [9]. Moreover, Liu et al. [10] (2010) found that the direct associations between polycyclic aromatic hydrocarbon (PAH), benzene and toluene (BT) metabolites decreased lung function.

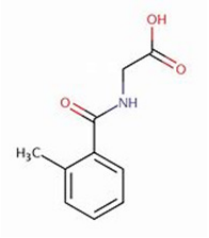
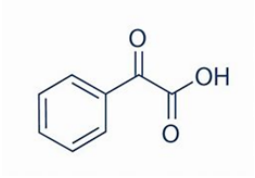
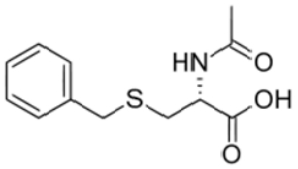
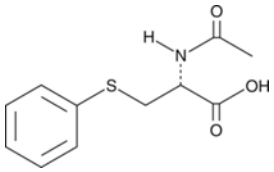
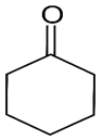
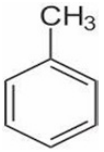
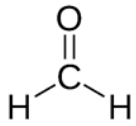
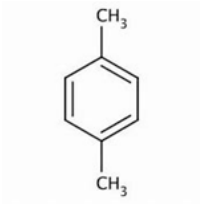
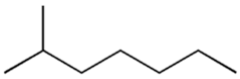
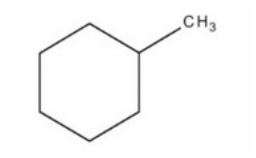
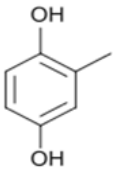
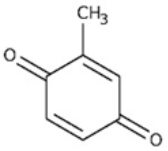
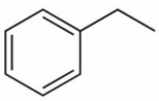
On the other hand, PAHs and BTs exposure could increase the risk of asthma in children. Some results have shown that asthmatic children have higher levels of malonaldehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) compared with healthy children [11].

Additive use of inhalants is second place in children, adolescents and adults of all addictions (Table 1). In Mexico, COVID-19 pandemic has led to an increase in the number of people and frequency of inhalation of solvents in the population [12]. Among the most used solvents of abused is thinner [13]. The major compounds identified in the thinner, with peak area >2%, were p- xylene 6%, toluene 4%, 2,4-dimethylheptane 3%, 2-methylheptane 2%, methylcyclohexane 2.75%, cyclohexanone 2.6% and nonane 2.1%.

The main damage caused by these substances is due to their high content of toluene (60-70% thinner) [14]. This psychotropic component is considered in the morbidity associated with this addiction [15]. Inhalation of toluene vapor generates psychotropic effects [16] and may induce male reproductive dysfunctions and carcinogenicity for its ability to decrease epididymal sperm counts and serum concentrations of testosterone [17]. In addition, its toxicity decreases albumin, uric acid and urea levels; and increases creatinine, triglyceride, cholesterol and glucose levels. Simultaneous exposure to these substances brings about an increase in the activities of glutathione peroxidase (GPX), malondialdehyde dismutase (MDA) and superoxide dismutase (SOD) levels; and a massive tubular degeneration, tubular cell vacuolization, glomerular disorganization, congestion and glomerular cell shrinkage in the kidney tissue [18]. Likewise, it increases the levels of TBARS, GSSG, GST, SOD, COX-2 and caspase-3 activity, and considerably decreases GSH, GR and GPx. In fact, the brain (cortex and cerebellum) is the most affected organ in this addiction [19].

The damage of DNA genes by minor metabolites of toluene, methylhydroquinone and methylbenzoquinone suggests the formation of 8-oxo-7 and 8-dihydro-2'-deoxyguanosine by metabolites of toluene, whose concentration increases in the presence of Cu (II) and NADH.

Table 1: Organic solvents and metabolites use to voluntary or involuntary innhalation

 Methylhyppuric acid	 Phenylglyoxylic acid	 S-Benzylmercapturic acid
 S-Phenylmercapturic acid	 Cyclohexane	 Toluene
 Formaldehyde	 Xylene	 2, -methylheptane
 Methylcyclohexane	 Methylhydroquinone	 Methylbenzoquinone
 Ethylbenzene	 Benzene	

Generation Of Free Radicals

UV-visible and ESR spectroscopies have been used to detect the generation of O (*-) (2) and semiquinone radicals [20]. Another process, which is used to establish contact with chemical solvents, is the chemical oxidation with hydroxyl radical (HO•) and sulfate radical ($SO_4^{\bullet-}$). These radicals are often used to treat water contaminated with aromatic compounds, ethylbenzene, toluene, benzene and xylene.

The initial phase of the oxidation process involves radical addition; hydrogen abstraction or one-electron transfer to the ring followed by reaction with O_2. The hydroxycyclohexadienylperoxy radical produced in this reaction can eliminate hydroperoxyl radical ($HO_2^{\bullet}$) to produce a phenolic compound, or it can rearrange to form a bicyclic peroxy intermediate that subsequently undergoes ring cleavage [21]. Recent studies with toluene and xylene showed that the concentrations of metabolites are individuated, miR-589-5p, miR-941, miR-146b-3p and

miR-27a-3p, with well-known implications in oxidative stress and inflammation processes [22], and cause adverse effects on pulmonary function in occupationally exposed workers [23]. These workers show reduction of forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC), and forced expiratory flow at 25-75% of FVC.

Inhalants are widely used as recreational drugs and toluene is the main chemical compound present in them. This substance is responsible for inducing redox imbalance at the neuronal level. It has been documented those alterations in oxidative balance could represent an intermediate signaling pathway in the cascade of effects induced by toluene [24].

Tissue Damage Targets

Toluene is highly lipophilic in nature and this makes it potentially harmful to the nervous system [25,26]. This solvent, in acute dose, modifies the composition of lipids and interacts with membrane lipids by increasing significantly Na^+, K^+-ATPase activity [27], thus increasing the intracellular Na^+. The increase in the intracellular Na^+ leads to an increase in Na^+/Ca^{2+} exchange. Also, increased Na^+ concentration produces electrical disturbance, which may result in arrhythmia. In addition, increased Ca^{2+} may affect proteases and may help in the conversion of xanthine dehydrogenase to xanthine oxidase; thus, leading to increased production of super oxide radicals. Another important effect of toluene is its accumulation in the cell membrane, which impedes transport of ions and solutes through it. In addition, toluene leads to the formation of oxygen radical, which reacts with unsaturated fatty acids and proteins in erythrocytes and provokes lipid peroxidation and protein breakdown as well as increase osmotic fragility [28]. Oxidation of plasma membrane lipids leads to autocatalytic chain reactions, which eventually alter the permeability of the cell [29].

In vivo exposure to high concentrations of toluene generates a dose-dependent elevation of oxygen reactive species in different organs by significantly increasing protein carbonyls in both the frontal cortex and cerebellum. Moreover, toluene exposure induces oxidative stress in the brain and this may be a component of an adverse outcome pathway for some of the neurotoxic effects [30]. In summary, toluene leads to the generation of free radicals and increases lipoperoxidation. In addition, it leads to the formation of antioxidant enzymes such as total antioxidant substances (TAS), superoxide dismutase (SOD), γ-glutamylcysteine synthetase (γ-GCS), glutathione transferase (GST), glutathione peroxidase (GPX) and glutathione reductase (GRD) [31]. Likewise, PFT-μ and PFT-α provide neuroprotective actions through regulation of oxidative stress and neuroinflammation [32].

Human toluene exposure increases CYP2E1 mRNA and modifies its activity in leucocytes as key factors for unraveling the sub cellular mechanisms of toxicity exerted by oxidative stress [33].

Addiction to this substance and to the solvents, in general, mainly affects the less favored classes of the society that have some degree of malnutrition [34], and implies a persistent oxidant load [35]. Individuals with different immunogenetic backgrounds have different sensitivities to toxic chemical exposure and have allergic stimulation that may influence the threshold for toluene sensitivity due to the modulation of neurotrophin-related genes [36]. Following exposure to the aromatic compounds, the expression level of COX-2 increases markedly. In addition, prostaglandin E (2) (PGE (2)) and prostaglandin F(2α) (PGF(2α)), major products of the COX enzyme, were found to be upregulated in response to toluene [37]. The author suggests that toluene induces the production and secretion of PGE (2) and PGF(2α) in lung epithelial cells via p38 MAPK and COX-2 activation in a redox sensitive manner.

Vulnerability To Alter Immune Response

Gasoline station workers, abundant in all the countries, have shown elevated protein carbonyl (PCO) levels and pro-inflammatory cytokines, decreased expression of CD80 and CD86 in monocytes, and reduced glutathione S-transferase (GST) activity. In other areas of work, the influence of organic solvents on the immunological, inflammatory and oxidative stress biomarkers has been demonstrated [38]. In fact, humans can be exposed to organic solvents by occupational exposure or by intentional inhalation for addiction or due to COVID-19 pandemic by the multiple and frequent use of disinfecting solvents.

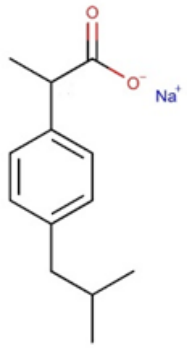
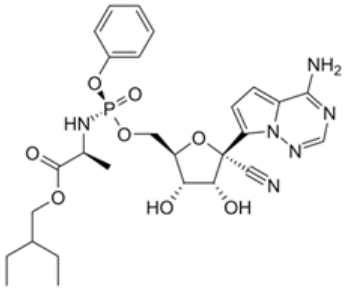
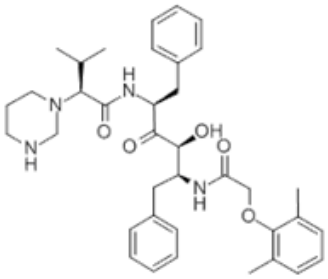
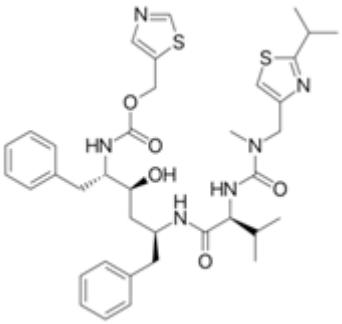
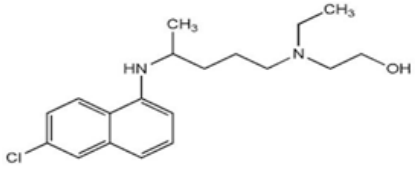
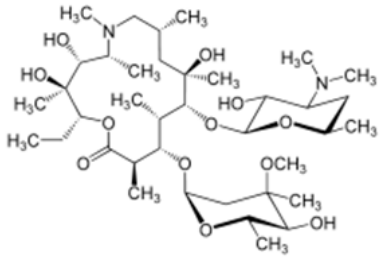
The global impact of the new coronavirus, has been evident in the last months for the unprecedented socioeconomic disruption and for more than 3.4 million deaths, which it caused in the world and which has registered a toll of more than 284,000 deaths in Mexico [39]. Coronavirus disease 2019 (COVID-19) is a kind of viral pneumonia whose unusual outbreak started in Wuhan, China, and later found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its rapid and global spread led to overwhelming inundation of hospitals with patients. In the course of researches to combat the infection,

FDA approved remdesivir for the treatment of the infection. Other off-label medications used in combating the infection include chloroquine and hydroxychloroquine, tocilizumab, lopinavir/ritonavir, favipiravir, convalescent plasma therapy, azithromycin, vitamin C, corticosteroids, interferon and colchicine [40].

Antivirals And Other Drugs Used

Currently, there is no licensed antiviral treatment to prevent human CoV infection. In the case of COVID-19, clinicians have identified its impacts on multiple organ systems, including gastrointestinal, renal, cardiovascular, pulmonary, immunological and hematological systems [41]. It is very important to identify and control risk factors of Covid-19 in susceptible subjects for successful treatment and prevention (Table 2). Based on these findings, the following drug therapies have been employed for its management:

Table 2: Drugs use to Covid-19 treatment

 Na-Ibuprofenate	 Remdesivir	 Lopinavir
 Ritonavir	 Hydroxychloroquine	 Azithromycin

Na-Ibuprofenate

Na-Ibuprofenate, has an amphipathic molecule capable of inserting into the bilayer membranes of the virus to destabilize its structure, alter its biological properties and prevent its duplication or infection. Its ant virucidal activity on Covid-19 leads to considerable reduction in local inflammation in the airways by inhibiting cyclooxygenase enzyme and by markedly diminishing reactive oxygen species (ROS). Its effectiveness in the treatment of COVID-19 infection suggests that reorganization of the actin filaments is a key step in lung inflammation induced by systemic inflammatory responses caused by SARS-CoV-2, and that the interaction between actin proteins and S1 is involved in the 2019-nCoV infection and pathogenesis [42].

Remdesivir

Remdesivir is an adenosine analogue that can target the RNA-dependent RNA polymerase and block viral RNA synthesis. The active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production. RNA-Dependent RNA Polymerase of

SARS-CoV-2 arrest of RNA synthesis occurs after incorporation of three additional nucleotides [43]. Remdesivir supplementation suppresses the systematic and hepatic inflammation by reducing inflammatory cytokines and by blocking nuclear factor κB (NF-κB) signaling [44]. However, neither antiviral nor immunomodulatory therapy in patients with SARS-CoV-2 infection/COVID-19 or pre-exposure prophylaxis against SARS-CoV-2 has proved to be effective [45].

3CLpro is a major CoV protease that cleaves the large replicase polyproteins during viral replication and can be targeted by the protease inhibitor lopinavir/ritonavir. In particular, several cases of recovered patients have been reported after being treated with lopinavir/ritonavir, which is widely used to treat Human Immunodeficiency Virus (HIV) infection in combination with the anti-flu drug oseltamivir [46].

Chloroquine (Cq)/Hydroxychloroquine (Hcq)

These drugs have the capacity to impair the replication of SARSCoV-2 by multiple mechanisms and their immunomodulatory properties could ameliorate clinical manifestations that are mediated by immune reactions [47].

HCQ activates the innate immune signaling pathways of IFN-β, AP-1 and NFκB. It knocks down mitochondrial antiviral signaling protein (MAVS), inhibits TANK binding kinase 1 (TBK1)/inhibitor-κB kinase ε (IKKε) and blocks type I IFN receptor that reduces the efficiency of HCQ against DENV-2 infection. Furthermore, HCQ significantly induces cellular production of reactive oxygen species (ROS) associated with host defense system. Suppression of ROS production attenuates innate immune activation and anti-DENV-2 effect of HCQ [48]. On renal dysfunction, HCQ markedly reduces macrophage and neutrophil infiltration, pro-inflammatory cytokine production and NLRP3 inflammasome activation, inhibiting it by down-regulating I/R or H/R-induced NF-κB signaling [49].

Chloroquine (CQ) and Hydroxychloroquine (HCQ) share similar chemical structures and mechanisms of action. CQ is widely used to treat malaria [50]. These authors found that COVID-19 infections are highly pandemic in countries where malaria is least pandemic and are least pandemic in nations where malaria is highly pandemic. Thus, putting forward their hypothetical benefits as efficacious means to treat COVID-19 infections. However, CQ and HCQ have the potential to cause harm as well as induce a broad range of adverse events that include serious cardiac side effects when combined with other agents. For patients with COVID-19, the impact of HCQ on cytokine production and suppression of antigen presentation may have immunologic consequences that hamper innate and adaptive antiviral immune responses [51].

Azithromycin (AZ)

Some hospitals have begun to use AZ in combination with HCQ or CQ for the treatment of COVID-19. The doses commonly employed in this regard are 500 mg of AZ on day 1 followed by a daily dose of 250 mg for the next four days + 200 mg of HCQ administered three times per day for ten days [52]. Azithromycin and hydroxychloroquine perform similar action as an acidotropic lipophilic weak base, capable of penetrating into cells, and inducing mild adverse events [53,54]. However, both drugs were not found to have association with survival benefit among hospitalized COVID-19 patients. Nonetheless, it is suggested that the combination of Zn supplement with CQ in the treatment of COVID-19 yields favorable result. This is because chloroquine enhances the effectiveness of Zn, since it acts as an ionophore for Zn, which, once inside an infected cell, stops SARS-CoV-2 replication [55].

Tocilizumab (Tcz)

This drug is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is used as pro-inflammatory cytokine and represents a major breakthrough for the treatment of immune-mediated disorders [56]. The immune activation responsible for high remission rates is also responsible for the unique treatment-related toxicity of cytokine release syndrome (CRS). The clinical signs of CRS include fever, hemodynamic instability, and capillary leak associated with T-cell activation and elevated cytokine levels. Tocilizumab, an anti-IL-6 receptor antagonist, provides control of severe CRS without being directly T cell toxic [57]. The drug has demonstrated to have a trend association towards reducing the mortality rate among ICU patients [58]. However, a large clinical trial is needed to confirm tocilizumab's clinical efficacy and safety on COVID-19 patients.

Ivermectine

Ivermectine is an antiparasitic drug that has shown effective pharmacological activity towards various infective agents, and which has been recommended for COVID-19 treatment [59]. Its drug has been reported to cause cell death in cancer cell lines by inducing PAK1-mediated cytostatic autophagy, caspase-dependent apoptosis and immunogenic cell death

(ICD) through the modulation of some pathways, including the WNT-T cell factor (TCF), Hippo and Akt/mTOR pathways. Moreover, it affects the growth and proliferation of cancer cells. In addition, it plays several different roles, such as RNA helicase function, small-molecule mimetic of the surface-induced dissociation (SID) peptide, an activator of chloride channel receptors, an inducer of mitochondrial dysfunction and oxidative stress [60].

Oxidative Stress and Viral Infection

The SARS-CoV-2/COVID-19 pandemic is one of the largest challenges in medicine and health care worldwide. In the absence of a vaccine and specifically designed drugs, the medical community has proposed the use of various previously available medications in order to reduce the number of patients requiring prolonged hospitalizations, oxygen therapy and mechanical ventilation; and to decrease the high mortality rate resulting from the disease [61]. SARS-CoV-19 infection is accompanied by severe pneumonia, pulmonary alveolar collapse and detention of oxygen exchange. Excess oxygen induces free radicals (FR). Free radicals promote cytotoxicity that leads to cell injury. In addition, they trigger mechanism of inflammation by mediating the activation of NFkB and induce transcription of cytokine production genes. Release of cytokines enhances the inflammatory response. Oxidizing agents come from phagocytic leukocytes such as neutrophils, monocytes, macrophages and eosinophils that invade the tissues. Oxidative stress (OS) represents an imbalance between the production and manifestation of reactive oxygen species therefore; the inability of the biological system to readily detoxify the reactive intermediates or repair the resulting damage [62] may enhance this stress. OS is elevated during critical illnesses and this contributes to organ failure. In COVID-19 disease, there is an intense inflammatory response known as a cytokine storm that could be mediated by oxidative stress [63]. Reactive oxygen species (ROS) play physiological roles as second messengers, but can also exert detrimental modifications on DNA, proteins and lipids when they are originated from enhanced generation or reduced antioxidant defense (oxidative stress). Formation and resolution of venous thrombus (DVT) are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, as well as the regulation of effector cells such as platelets, endothelial cells, erythrocytes, neutrophils, mast cells, monocytes and fibroblasts [64].

Immune cells, particularly neutrophils, protect the humans against pathogens; such as bacteria, fungi and viruses; through increased generation of free radicals or oxidants and neutrophil extracellular traps (NETs) that ensnare pathogens, killing them extracellularly. NET levels increase during pro-inflammatory diseases. It is found that depending on disease severity, COVID-19 patients exhibit elevated NET levels. Probably drugs inhibiting oxidant formation, such as vitamin supplements, could decrease NET formation in animal models of inflammation [65]. Therapeutic potential of vitamins A, C, D, E supplement and micronutrients in COVID-19 ameliorate the inflammation and oxidative stress associated with the disease [66].

Vitamin B3 or niacin is one of the most important compounds of the B-vitamin complex, which performs a number of pivotal functions that ensure homeostasis. This role can be attributed to the gut microflora and its ability to shape human behavior and development by mediating the bioavailability of metabolites. This fact may be the possible interconnection between the novel coronavirus and commensal bacteria and explains how the gastrointestinal deficiencies displayed by SARS-CoV-2-infected patients arise [67].

A healthy diet may be considered a reliable tool for maintaining and optimizing our key internal parameters and could help SARS-CoV-2 patients.

Ozone Therapy

Systemic ozone therapy (OT) could be potentially useful in the clinical management of several complications secondary to SARS-CoV-2. It is highly effective for decreasing organ damage mediated by inflammation and oxidative stress. Homeostasis of the free radical and antioxidant balance by OT are associated with its ability to modulate NF-κB/Nrf2 balance and the expression of IL-6 and IL-1β [68]. Therefore, ozone therapy could mitigate SARS-CoV-2-induced complications and decrease mortality.

Expectations

Since the recovery/death ratio of SARS-CoV-19 infection has significantly increased in different nations of the world in the last weeks, it becomes clear that the experimental antiviral therapy together with antioxidant drugs, oxygen and dietary support, and the availability of intensive care unit beds in hospitals with rigorous government control measures, all play an important role in dealing with this lethal virus. In fact, it is very import-

ant to identify and control the risk factors of COVID-19 in susceptible subjects. This would guarantee success in the treatment of the disease and its prevention, as well as reduce the voluntary and involuntary exposure to toxic solvents that are abundantly and widely present today, both at home and work places, as an effort to prevent the infection, or avoid unexpected sequelae of the COVID-19 pandemic. With the global COVID-19 pandemic, this exposure has become an increasing concern to the health sector worldwide.

Declarations

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Conflict of interest: The authors declare that they have no conflict of interest.

Authors' contributions

DCG[a,b,c,d], NOB[b,c,d], MOH[b,c,d], GBM[b,c,d], AVP-[b,c,d], MPS[b,c,d], HJO[b,c,d]

(a) Contributed to conception. (b) Critically revised the manuscript for important intellectual content. (c) Drafted manuscript. (d) Gave final approval. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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