



Drinking water pollutants may affect the immune system: concerns regarding COVID-19 health effects

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Abstract

The current coronavirus pandemic is leading to significant impacts on the planet, changing our way of life. Although the COVID-19 virus mechanisms of action and pathogenesis are still under extensive research, immune system effects are evident, leading, in many cases, to respiratory distress. Although apparent pollution reduction has been noticed by the population, environmental and human health impacts due to the increased use of plastic waste and disinfectants is concerning. One of the main routes of human exposure to pollutants is through drinking water. Thus, this point of view discusses some major contaminants in drinking water known to be immunotoxic, exploring sources and drinking water routes and emphasizing the known mechanisms of action that could likely compromise the effective immune response of humans, particularly raising concerns regarding people exposed to the COVID-19 virus. Based on a literature review, metals, plastic components, plasticizers, and per- and polyfluoroalkyl substances may display the potential to exacerbate COVID-19 respiratory symptoms, although epidemiological studies are still required to confirm the synergistic effects between these pollutants and the virus.

Keywords SARS-CoV-2 · Immune response · Cytokines · PFAS, plastic components and plasticizers · Metals

Introduction

The current coronavirus pandemic is resulting in huge impacts worldwide in many aspects. With social distancing and mandatory self-quarantines in order to avoid the spread of the novel COVID-19 coronavirus and, consequently, relieve the burden of the healthcare system to save lives, the population has been falsely convinced that there have been environmental benefits with decreased environmental pollution. In fact, in very industrialized countries and cities, clear skies and more wildlife roaming the streets and in rivers have been spotted, as the pandemic has led to decreased car and flight transit, as well

as the shutdown of industries and commerce, forcing people to stay at home (National Geographic 2020). However, the COVID-19 pandemic, in reality, has been causing major drawbacks in terms of environmental protection policies around the globe. For example, the United States Environmental Protection Agency (U.S. EPA) has stopped enforcements concerning monitoring and reporting requirements of environmental protection for an undefined period of time, China has temporarily suspended environmental regulations, and Brazil has reduced surveillance on environmental compliance in the Amazon Rainforest (Forbes 2020). At the same time, the fear associated with COVID-19 transmission has resulted in increased use of single-use plastics, disinfecting products and related chemicals, therefore causing increased environmental water pollution concerns. Single-use plastics are now more popular than ever as, amid the COVID-19 fear, people will preferentially buy disposable items like water bottles and other products housed in plastic containers and bags, such as hand sanitizers, sanitizing wipes, toilet papers, cleaning products and tissues, and food items.

The current situation has been even more aggravated since recycling companies and the plastic collection points of 100,000 retailers worldwide have ceased operations, not only due to health and safety concerns, but also for financial

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reasons, with the costs concerning gathering the waste and processing higher than simply producing more plastic (Haultail 2020). In addition, since 2018, China and other countries have stopped accepting millions of tons of recyclable materials and waste from the USA for processing, which leads to major waste management issues in the country (Huffpost 2018).

Governments worldwide have taken precautionary measurements to reduce COVID-19 infections. In Surabaya, Indonesia, one of the responses to the coronavirus pandemic was a drone dispersing clouds of disinfectant in the sky above the city (Wardoyo and Geddie 2020). Although COVID-19 is a contagious respiratory disease that spreads through droplets from the nose or mouth via coughing or sneezing, this type of approach could be even more toxic to people, since disinfectants such as bleach and glutaraldehyde have been reported as leading to higher risks for the development of progressive lung diseases (Svanes et al. 2018; Dumas et al. 2019) and do not necessarily improve virus containment.

Studies on COVID-19 transmission and mode of actions are still very incipient to draw any definitive conclusions, but reports have shown that older adults and people with previous underlying medical conditions like lung or heart disease or diabetes seem to be at higher risk for developing more serious complications from this disease (Onder et al. 2020; Zhou et al. 2020).

One of most recent explanations of the deadly effects of COVID-19 is associated to its immune system effects, in a phenomenon broadly known as “cytokine storm,” where the immune system releases a large number of cytokines, which attack the organs they were intended to protect (Shi et al. 2020). The effects of this immune system overreaction can lead to fatal outcomes due to complications such as lung inflammation, pneumonia, and respiratory issues.

Numerous contaminants are present in the aquatic system, and many of these are frequently found in our drinking water and are known carcinogenic and immune suppressors, raising concerns on the health effects associated with the new coronavirus. Therefore, this manuscript identifies the major inorganic and organic pollutants found in drinking water that have been associated to adverse immune system effects, exploring human exposure routes and mode of action on the immune system, addressing concerns regarding the potential health impacts on people exposed to COVID-19. The health risks associated with extensive use of disinfectants and cleaning products are also discussed.

Major inorganic and organic water pollutants known to affect the immune system

Due to the finite nature of the world's fresh water sources, water quality is of utmost concern. Expanding populations

allied to continued growth in the manufacturing, pharmaceutical, and chemical sectors increase the potential for exposure to a diversity of chemical compounds through air, food and, especially, water. Access to clean water is crucial in our daily lives, from water used to wash our food, to showering, swimming, and drinking. Drinking water pollution is not recent or new and has been linked to several water-borne diseases (Levantesi et al. 2012; Luby et al. 2015) and may result in autoimmune diseases in humans (Leffel et al. 2003). Common drinking water pollutants include metals, such as arsenic, lead, and mercury, and organic chemicals like poly and per- and polyfluoroalkyl substances (PFAS) and phthalates, as well as microbes and cysts.

While water treatment plants are capable of eliminating some of these pollutants, others are poorly removed and may contaminate drinking water. Growing concerns are noted, especially regarding emerging contaminants with endocrine disrupting properties, which can mimic, block, or interfere with hormones, producing adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife (Diamanti-Kandarakis et al. 2009). Herein, we will focus on selected pollutants considered major contaminants in drinking water which are expected to show increased levels during and after the COVID-19 pandemic and result in adverse effects to the immune system. Contaminants such as chlorinated hydrocarbons, although also major water pollutants, are not expected to increase during the pandemic, as fewer agricultural activities are being carried out, due to human exposure concerns regarding the coronavirus, and were, thus, not included.

Metals

Among the metals regularly monitored in public water supplies and with established maximum contaminant levels determined by the U.S. EPA in drinking water, arsenic (As), cadmium (Cd), chromium (Cr), lead (Pb), and copper (Cu) have been identified as pollutants of concern, posing a serious threat to human health.

The most ubiquitous of the toxic metals in drinking water is Pb. Pb, as well as Cu, can leach from water pipes and soldered joints in either the distribution system or individual houses, being an issue especially in homes with older infrastructure (ATSDR 2002; Makris et al. 2014). Pb exposure has been associated with a wide range of adverse effects in humans, including blood disorders in adult and children (Farzan et al. 2018), gastrointestinal distress, decreased neurological functioning, heart and kidney diseases (IARC 2006; WHO 2011a), and immune function alterations, especially in young children (Goebel et al. 2000; Li et al. 2005; Chakrabarty and Sarma 2011). The EPA's maximum contaminant level (MCL) for Pb is 0.005 mg L⁻¹ in water. However, several studies have indicated that Pb exposure has negative human health impacts

even at very low levels and that there is no safe threshold value for this contaminant in drinking waters (Haeffliger et al. 2009; Wang et al. 2019). Exposure to Cu, even at low doses, has been correlated to mutagenesis, carcinogenicity, infertility, and immune suppression (Kvietkauskaitė et al. 2004; Markevičius and Dringeliene 2004). The MCL for Cu in drinking water is 1.3 mg L^{-1} .

As is used industrially as an alloying agent, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, wood preservatives, in pesticides, feed additives, and pharmaceuticals (NRC 1999; Flanagan et al. 2012). The greatest threat to public health from inorganic As originates from contaminated groundwater and drinking water, where high levels have been observed in several countries, including Argentina, Bangladesh, Chile, China, India, Mexico, and the USA (NRC 1999; Flanagan et al. 2012). Exposure to As is associated to adverse effects during pregnancy and infant mortality and negative impacts on cognitive development, diabetes, pulmonary and cardiovascular disease, cancers, heart attacks, and kidney failure (Farzan et al. 2013; Tolins et al. 2014; Quansah et al. 2015). The effect of As in the immune system has been demonstrated in many studies, including increased risk of respiratory infections (Rahman et al. 2011; Cardenas et al. 2015, 2018; Farzan et al. 2016, 2018). The MCL for As in drinking water is 0.010 mg L^{-1} .

Contamination of drinking water may occur as a result of the presence of Cd as an impurity in the Zn of galvanized pipes or cadmium-containing solders in fittings, water heaters, water coolers, and taps (WHO 2011b). Human exposure to Cd could cause organ system failure, bone, and cardiovascular system damage, renal toxicity, neurotoxicity, diabetes, and cancer (Satarug et al. 2010), as well as immune system impacts (Skoczyńska et al. 2002). The MCL for Cd in drinking water is 0.005 mg L^{-1} .

Cr and its salts are used in mining, chrome plating, cement production, leather tanning, detergents, pigments and paints, photography, fungicides, in the ceramic and glass industry, and for corrosion control (WHO 2003). Solid wastes from chromate-processing facilities, when disposed of improperly in landfills, can be groundwater contamination sources, with a Cr residence time of several years (WHO 2003). Cr(VI) and Cr(III) are the most stable oxidation states of this element. While Cr(III) is a proposed essential nutrient, Cr(VI) is predominantly produced during industrial activities. The presence of Cr(VI) in drinking water sources is of health concern, since exposure to Cr(VI) has been known to adversely affect the liver and kidney, the respiratory and alimentary tracts, and the hematological and immune systems (Shrivastava et al. 2002; Wilbur et al. 2012; Shipkowski et al. 2017), leading to its classification as a carcinogenic compound (Bucher 2007). The MCL for Cr in drinking water is 0.05 mg L^{-1} .

PFAS

PFAS, also known as forever chemicals, have been categorized as compound classes of increasing concern regarding drinking water exposure. Their unique chemical properties, comprising persistence, resistance, and their ability as water and oil repellents, make these substances commercially attractive, with several applications used in consumer products, including surfactants, water repellents sprays, lubricants, adhesives, additives and coatings, paints, and firefighting foams (Prevedouros et al. 2006; Schaidler et al. 2017). They are, therefore, found in food packaging, non-stick products, stain-repellent clothing, cleaners, and many other household items. Groundwater contamination near military bases and airports due to the use of firefighting foams is of great concern and considered one of the major sources of PFAS (Moody and Field 2000; Hu et al. 2016).

Due to their amphiphilic properties, and preferential binding to proteins, PFAS have been found to be the most prevalent contaminants in human blood (Kannan et al. 2004) and wildlife worldwide (Keller et al. 2005; Francis et al. 2008; Quinete et al. 2009), presenting clear potential hazards to human health. Human exposure to PFAS can occur through food and water ingestion, dust inhalation, and hand-to-mouth transfer from contaminated area (Crone et al. 2019; Sunderland et al. 2019). Studies have shown that human PFAS exposure has been linked to elevated cholesterol, obesity, cancer, developmental delays, thyroid disease, and infertility and immune suppression in children (Ganesan and Vasudevan 2015; Pennings et al. 2016; Sunderland et al. 2019). More recently, De Toni et al. (2020) observed increased cardiovascular risks associated with chemical sensitivity to perfluorooctanoic acid (PFOA), therefore suggesting that increased PFOA levels in the blood may lead to cardiovascular diseases. It is important to highlight that after the phase down of the production of “legacy” PFAS, PFOA and perfluorooctane sulfonate (PFOS), which have replaced these compounds, are still poly or per-fluorinated compounds, presenting shorter chains or the insertion of ester functional groups (Clara et al. 2009) and a major gap concerning the understanding of the toxicity effects and pathways of these compounds in humans, and the environment is clear. The U.S. EPA’s lifetime health advisory limit in drinking water for PFOS and PFOA is of 70 ng L^{-1} (EPA 2009).

Plasticizers and plastic components (phthalates and bisphenols)

Phthalates and bisphenol A (BPA) are commonly called “everywhere chemicals,” as they are common in the countless plastic products of daily use (Trivedi et al. 2020).

Phthalates are chemicals of emerging concern widely used as plasticizers and additives in many consumer products,

including pharmaceuticals, cosmetics, personal care, medical and building materials, food packing, detergents, and children's toys (Schettler et al. 2006; National Research Council 2008). They are also used as solvents and lubricants and are found in many spray products, such as pesticides, fragrance products, and hairspray, among others. These phthalic acid esters are lipids with different alkyl groups that present varying hydrocarbon chain lengths, making them poorly soluble in water, displaying slow degradation rates while, as additives, they are non-covalently bound to the material matrix, eventually reaching the surface and leaching from the product, resulting in environmental accumulation (Díaz Padín et al. 2019). These are the most common chemicals which humans are in contact with (Net et al. 2015), and exposure occurs mainly via ingestion, inhalation, dermal contact, contact with dust/soil, and parenteral administration (National Research Council 2008; Net et al. 2015; Wang and Kannan 2019). Previous assessments have associated phthalates with diabetes and insulin resistance (Stahlhut et al. 2007; Sun et al. 2014), overweight and obesity (Buser et al. 2014), allergy and asthma (Braun et al. 2013; Hoppin et al. 2013), anomalies in development and reproductive health (Duty et al. 2003; Frederiksen et al. 2012; Upson et al. 2013), hepatic and renal function, hepatic structure, thyroid signaling, immune function, and metabolic homeostasis (Rusyn et al. 2006; Wei et al. 2012; Shehata et al. 2013). The phthalate metabolites bis(2-ethylhexyl) phthalate (DEHP) and benzyl butyl phthalate (BBP) have been classified as probable and possible human carcinogens, respectively, by the U.S. EPA (Wang and Kannan 2019). A maximum admissible concentration for DEHP in water of $8 \mu\text{g L}^{-1}$ and $6 \mu\text{g L}^{-1}$ was established by WHO and U.S. EPA, respectively (WHO 2004; EPA 2018a) (EPA 2009).

Bisphenol A (2, 2 bis(4-hydroxyphenyl) propane, BPA) is used in the manufacture of polycarbonate plastics present in many commonly used consumer goods, i.e., plastic containers, toys, water bottles, and baby pacifiers, among others. During use, this compound leaches from products, resulting in high human and animal exposure worldwide (McLachlan 2001; Rochester 2013). BPA is an endocrine disruptor, with the ability to bind to estrogen receptors and promote both agonist and antagonist activity (Hiroi et al. 1999). It also displays the ability to cross the placental barrier, which is of concern regarding developmental responses (Imanishi et al. 2003; Mørck et al. 2010), and appears to activate many immune pathways involved in both autoimmune disease development and autoimmune reactivity provocation (Kharrazian 2014).

Although BPA-containing products have slowly been taken off the market, due to endocrine disrupting concerns, replaced by analogs, such as bisphenol S (BPS), little is known about their immune effects, requiring further assessments (Xu et al. 2016).

Exposure pathways: Route to drinking water and human exposure

Drinking water is derived from either surface waters, comprising rivers, streams, wetlands and lakes, or groundwater, consisting of the water contained beneath the surface in rocks and soil accumulated underground in aquifers (Khublaryan 2009).

Several contaminants of public health importance are naturally occurring in these water bodies. For example, metals may originate from natural geochemical lithosphere conditions and geological processes, such as volcanic action, related hydrothermal activity, and weathering (Garrett 2000). Anthropogenic activities, however, have led to extensive contamination of both sources by thousands of chemical substances (Holt 2000; Howard et al. 2006), which may be released in many stages, including their extraction, manufacture, formulation, use, and end-user disposal or destruction (Holt 2000).

In general, urbanization and industrialization processes and agriculture and forestry activities are considered the two major contaminant inputs for these freshwater water bodies (Holt 2000). Contaminant sources from these inputs may be classified as point source pollution (PS), easily identified and confined locations, or non-point source pollution (NPS), resulting from many diffuse sources (EPA 2018b). The former comprises domestic sewage networks, industrial effluents, and accidental spills, while the latter consists of agricultural practices, scattered dwellings, atmospheric deposition, construction work, land run-off, and river transportation (EPA 2018b). Both result in differential contaminant discharges to water bodies, with PS usually consisting of direct discharges to water courses, while NPS may involve partial contaminant deposition before reaching the water course (Holt 2000). It has been reported that NPS is the leading cause of water quality problems, as significant variations over time and space are usually noted, reflecting seasonal use patterns (Holt 2000; EPA 2018b).

Concerning sources of contamination, surface water contamination occurs mostly through direct or indirect emissions and groundwater can be contaminated by soil leaching (WHO 2016). Groundwater contamination, in particular, comprises a significant public health concern, as this is an important source of drinking water in many regions worldwide, many times the only one, constituting 97% of global freshwater (Howard et al. 2006).

Surface waters mainly contaminated by domestic and industrial sewage are treated by municipal water treatment plants (WTP). WTP are designed to remove conventional organic pollutants found in domestic and industrial wastes, although many lacks the capacity to remove several contaminants (Li 2014). This has, in fact, been recognized as the main introduction route for several contaminants into the aquatic

environment, since they are not treatment targets (Ternes 1998; Bolong et al. 2009).

It is important to note that contaminant emission patterns and amounts vary among chemicals. For example, pharmaceutical production processes using intermediates release only small amounts into the environment, end-use products, such as household detergents are almost 100% released into public sewers, while chronic water body contamination is observed in the case of plastic components and plasticizers, due to leaching from plastic houseware and utensils, among others (Erythropel et al. 2014). It is also important to note that potable water supply treatment and the distribution system themselves may also result in contaminant inputs in drinking water, due to, for example, disinfection processes, which produce several toxic by-products (Holt 2000), and certain metals, i.e., lead, from brass plumbing and other distribution network materials; organotins, from polyvinyl chloride pipes and PAHs from older pipes, lined with coal tar pitch (Forsyth and Jay 1997; Elfland et al. 2010; WHO 2011c).

Immune suppression effects of drinking water contaminants and COVID-19 concerns

Common COVID-19 symptoms comprise fever, fatigue, respiratory symptoms, lymphopenia, and pneumonia, while some reports also indicate gastrointestinal symptoms (Chan et al. 2020; Gu et al. 2020; Huang et al. 2020; Prompetchara et al. 2020; Wu et al. 2020). Immune responses of infected patients have not yet been fully elucidated, although several studies have indicated that lymphopenia and “cytokine storms,” a form of systemic inflammatory response syndrome, involving many specific inflammatory mediators, such as cytokines (i.e., IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF α , among others), which play a vital role in inflammatory reactions (Lee et al. 1994; Ramella et al. 2017), are also a major factor in the COVID-19 condition (Nicholls et al. 2003; Wong et al. 2004; Mahallawi et al. 2018; Shimabukuro-Vornhagen et al. 2018).

Many pollutants previously considered only in light of their endocrine disruption capability have recently also been implicated in the activation of several immune pathways involved in both autoimmune disease development and autoimmune reactivity provocation, as estrogen has also been reported as playing an important role in the immune system altering inflammatory mediator responses and humoral immune response (Lee et al. 1994; Yoshino et al. 2003; Haghmorad et al. 2014). These include contaminants such as metals; PFAS; plastic components, such as BPA; and plasticizers, like phthalates (Dong et al. 1998; Kharrazian 2014; Hansen et al. 2015), although studies are still incipient in this regard. Although many *in vitro* studies have demonstrated cytokine effects, among other immune responses by several pollutants

(Shertzer et al. 1985; Li et al. 2013), only assessments performed through the drinking water exposure route in mammals (mice, rats, rabbits) in laboratory conditions or concerning human cohorts are included herein.

Metals

Several studies have demonstrated that exposure to many metals, both toxic and essential, at both subchronic and chronic levels may result in immunotoxic effects, especially concerning cytokines. However, many assessments are performed *in vitro*, or when in mammals (mice, rats) through oral gavage or food pellet exposure, and drinking water exposure assessments are still scarce. In addition, the mechanisms responsible for these effects are still unclear.

In this context, the few assessments available in this regard all point to significant immunotoxic effects even at low doses. For example, exposure to lead (Pb) and copper (Cu) for 2 weeks through drinking water in has been reported as leading to alterations in the natural cytokine balance in BALB/c mice with free access to drinking water containing Pb and Cu. The animals displayed upregulation of interferon-gamma (IFN- γ), a homodimeric glycoprotein produced by activated T, B, and NK cells, in the spleen of both treated groups, while interleukin-4 (IL-4), a TH2 cytokine secreted by activated TH2 and NKT cells and a potent inducer for of CD4⁺ naive T cell differentiation into TH2 effector cells, was only upregulated in the Cu-treated group and downregulated in the Pb-treated group Pb. Thus, both Pb and Cu significantly altered natural cytokine balance, which may lead to negative immune effects (Radbin et al. 2014).

In another study, the effects of subchronic, oral, and low-dose cadmium (Cd) exposure (32 mg L⁻¹ cadmium chloride in drinking water for 10 weeks on the rat immune system) were evaluated, and the results indicate that Cd-exposed animals demonstrated slight increases in regulatory T cells and significant increases in the production of IFN γ and IL-10, suggesting that Cd exposure may affect multiple T cell subsets, impacting both immune cell function and cellularity, which may enhance inflammatory responses (Turley et al. 2019).

Regarding Cr, it has been noted that only a few data are available on pro-inflammation assessments for this element. In one laboratory study, exposure to 50 mg L⁻¹ or 200 mg L⁻¹ in the drinking water of 5-week-old pubertal male ICR mice for 7 and 21 days led to significant increases in serum TNF α and IL-6 in the 200 mg L⁻¹ treatment at 7 days exposure and increases in mRNA cytokine levels, suggesting that Cr displays immunotoxicity potential by altering inflammatory responses (Jin et al. 2016). In a human cohort assessment, occupational chromate exposure led to significantly decreased IL-6, IL-10, IFN- γ , IL-17A, and IFN- γ /IL-4, while significantly increased C3 and C4 expressions were observed. In addition, IFN- γ , IgG, and IgA displayed an inverse

association with whole blood Cr, while C3 and C4 were positively associated with whole blood Cr, and both IL-10 and IL-17A inversely associated with urine Cr. The results indicate that occupational exposure to chromate could downregulate the cellular and humoral factors of the immune system (Qian et al. 2013).

Concerning As, rabbits exposed to 13 mg L⁻¹ As₂O₃ in drinking water for 6 months resulted in the increased expression of vascular cell adhesion molecule-1, IL-8, and IL-6, key molecules involved in inflammation, at the RNA and protein levels, implicating this element in inflammatory mechanisms (Ma et al. 2012). In one of the few assessments carried out in humans concerning arsenic (As) exposure through drinking water, the immunological status of children (90 individuals, aged 6–10 years, comprising 38 girls, 52 boys) exposed to arsenic through their drinking water was assessed. Increased incidences of asthma, allergies, and parasitic infections in individuals with high As levels in urine compared with those with As levels lower than the reference value in urine (50 µg L⁻¹) were noted, and increased urine arsenic levels were associated to significantly inhibited IL-2 secretion levels. With these findings, the authors postulated that As exposure could alter T cell activation processes, leading to an immunosuppression status that would, in turn, favor opportunistic infections and carcinogenesis (Soto-Peña et al. 2006).

PFAS

Studies on PFAS immune effects are still scarce. One assessment evaluated developmental immunotoxic effects after maternal oral exposure through drinking water PFOS (perfluorooctane sulfonate) at 0.1, 1.0, and 5.0 mg PFOS kg day⁻¹ during gestational days 1–17 in C57BL/6 mice and reported that male pups were more affected than females since; an imbalance in TH1/TH2-type cytokines with excess TH2 cytokines (IL-4) was detected only in males at 8 weeks old, while hormone alterations were also noted, i.e., decreased serum testosterone levels and increased estradiol levels only in male pups. The authors postulate that testosterone-mediated endocrine function may be partially involved in the TH1/TH2-imbalance induced by PFOS (Zhong et al. 2016). In another assessment, NOD mice were exposed to perfluoroundecanoic acid (PFUnDA) through drinking water at 3, 30, and 300 µg L⁻¹ at mating, during gestation, and lactation and until 30 weeks of age. Altered cytokine secretion, namely INFγ, TNFα, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-13, and IL-17, in activated splenocytes was noted after exposure to 3 µg L⁻¹ PFUnDA. The authors hypothesized that the observed differences in cytokine secretion at different exposure doses could indicate a non-monotonic dose response, with different receptor activations or different receptors being activated at different exposure levels (Bodin et al. 2016).

Other assessments have also reported cytokine alterations, such as the study carried out by Fair et al. (2011), who exposed female B₆C₃F₁ mice to PFOS through drinking water for 28 days at total 0, 0.1, 0.5, 1, or 5 mg PFOS kg⁻¹ doses and noted significantly increased IL-6 production by B cells, and the assessment was performed by Zheng et al., who exposed adult male C57BL/6 mice to PFOS for 7 days and noted reduced Th1 cytokine (IL-2 and INFγ) secretion in favor of Th2 cytokines (IL-4, IL-10) (Zheng et al. 2011). The latter authors indicated that a host's immune state is likely to be characterized by a shift toward T(H)2-like state which may lead to cellular response suppression and humoral response enhancement following a high-dose short-term exposure to PFOS. In humans, several PFAS have been directly associated to asthma diagnosis or severity and number of common cold episodes, as well as reduced seroprotection from the influenza A H3N2 virus and higher IL-4 and IL-5 T-helper cytokine levels in humans (Dong et al. 2013; Granum et al. 2013; Humblet et al. 2014; Looker et al. 2014; Zeng et al. 2015; Zhu et al. 2016) while the upregulation of immunomodulatory genes has been associated with a range of prenatal PFAS exposure (Pennings et al. 2016).

Plasticizers and plastic components (phthalates and bisphenols)

In vivo assessments regarding exposure to drinking water in laboratory conditions are extremely scarce for phthalates. In one of the few evaluations carried out in this regard, BALB/c mice were exposed to butyl benzyl phthalate (BBP), a parent compound of the phthalate metabolite mono-*n*-butyl phthalate (MnBP) at 3 mg mL⁻¹ exclusively through drinking water for different time periods. Maternal exposure to BBP resulted in airway inflammation in the offspring, up to the F2 generation, mediated by BBP-induced DNA hypermethylation. CD4⁺ T cell function from the offspring of BBP-exposed dams indicated increased susceptibility for a T_H2-mediated immune response, while no significant changes in regulatory T cell functions were detected. The authors conclude that early exposure to specific phthalates increases susceptibility to the development of allergic asthma mediated by epigenetic changes, leading to altered expression of genes that play a crucial role in immune regulation, contributing not only to asthma development but potentially also to other immune-regulated diseases (Jahreis et al. 2018).

Concerning humans, a significant association between maternal urinary concentrations of the phthalate metabolite mono-*n*-butyl phthalate (MnBP) and increased asthma risk in children has been recently reported (Jahreis et al. 2018).

BPA exposure has been reported as affecting immune cell populations and function from both the innate and adaptive immune system, mainly through agonistic and antagonistic effects on receptors, which modulate the expression of several cytokines, resulting in altered T cell responses and

upregulated pro- and anti-inflammatory cytokines and chemokines (Xu et al. 2016). It has also been implicated as a contributor toward the development of type 2 diabetes mellitus, allergy, asthma, and breast cancer due to these immune function altering effects (Xu et al. 2016). However, a lack of studies is still noted.

Assessments have indicated that BPA administered through drinking water results in significant alterations in lymphocyte subpopulations, induction of inflammatory Th-1 type cytokines, and suppression of IL-4 in mice, indicating that BPA induces Th-1 polar shifts of transcription factor, resulting in heightened cellular immune responses leading to an exaggerated Th-1 immune response (Weaver et al. 2005). In another study, BPA was administered to mice through drinking water at 0.015, 1.5, and 30 mg mL⁻¹ for 4 weeks (Youn et al. 2002). A significant production of Th-1 type cytokine (IFN- γ) was induced while the Th-2 type (IL-4) was suppressed, suggesting stimulation of prolactin production by estrogenic BPA effects, affecting cytokine profiles, leading to imbalanced cellular immune response. In another assessment, mouse pups were exposed both during the prenatal and postnatal periods to 10 μ g mL⁻¹ of BPA in maternal drinking water displaying an asthma phenotype, while those only exposed in the postnatal period did not exhibit this condition, indicating that environmental exposure to BPA may be linked to the development of airway inflammation and allergic sensitization, although effects are probably modified by the exposure time period duration (Nakajima et al. 2012).

Although BPA has been substituted by BPS, BPA is persistent in sediments and more resistant to biodegradation than BPA in aquatic environments, leading to increased public health concerns (Herrero et al. 2018). Studies in mammals assessing exposure through drinking water, however, are almost non-existent. Of the few available assessments, one study exposed CD-1 mice from gestational day 8 to postnatal day 19 to at 200 μ g kg⁻¹ bw day⁻¹ of BPS and observed alterations in estrogen-responsive genes (Hill et al. 2017), while another evaluated the expression of estrogen receptor and tyrosine hydroxylase immunoreactive cells in two brain regions critical for maternal care in two generations of CD-1 mice and reported significantly increased expression of estrogen receptor in the caudal medial pre-optic area (cmPOA) that was significantly increased when female F0 were exposed to a BPS dose of 200 μ g kg⁻¹ bw day⁻¹, but the same phenomenon was not found in F1 generation (Catanese and Vandenberg 2017). No assessments specifically assessing more general immune responses, such as cytokines, however, are available for BPS.

Health risks associated to disinfectants and cleaning products

The coronavirus pandemic has completely changed our way of life, and the fear of COVID-19 spread has introduced a

more frequent use of chemicals and disinfectants. Most of the products used to disinfect against COVID-19 meeting EPA criteria contain the active ingredient quaternary ammonium (quats) (EPA 2020). Other active ingredients contained in mixtures are hydrogen peroxide, isopropanol, ethanol, sodium hypochlorite, octanoic acid, dodecylbenzenesulfonic acid, chlorine dioxide, phenolics, triethylene glycol, L-lactic acid, dichloroisocyanurate dihydrate glycolic acid, or hypochlorous acid. Some of these compounds, for example, the mixture of quaternary quats and sodium hypochlorite (bleach), have been shown to cause negative health effects when used regularly, especially since adequate use requires protection (gloves, good ventilation), something that people do not usually know about.

Longitudinal studies have shown that occupational exposures to cleaning agents, such as quats, results in a higher proportion of asthma cases in adults (Kogevinas et al. 2007; Obadia et al. 2009). Another study has found that the exposure of women through occupational and/or regular cleaning activities at home result in accelerated declines of lung function, which could represent long-term respiratory health problems (Svanes et al. 2018).

A recent study performed in the USA concerning female nurse exposure to specific disinfectants, such as glutaraldehyde (a strong disinfectant used for medical instruments), hydrogen peroxide, bleach, alcohol, and quats (used for low-level disinfection of surfaces such as floors and furniture), found that nurses were associated with an increased risk of chronic obstructive pulmonary disease (Dumas et al. 2019). These findings indicate concrete evidence of respiratory diseases due to disinfectant exposure. Although the importance and need for proper disinfection procedures in hospitals, especially during the COVID-19 pandemic, is clear, the health risks associated with cleaning product exposure should be considered.

Conclusions and required future studies

Due to the current need to address and understand the impact of different environmental exposures regarding COVID-19, relevant contaminants in drinking water, including metals, PFAS, and plasticizers, according to previously reported immunotoxicity, may raise potential concerns related to COVID-19 respiratory symptoms. Epidemiological studies are still required to evaluate potential synergistic effect between environmental pollutants and the virus. Previous studies have reported that, in addition to affecting the immune response, some compounds can also increase pathogen virulence or resistant to antibiotics, such as, for example, correlations between Pb exposure and greater detection of methicillin-resistant *Staphylococcus aureus* (MRSA) (Eggers et al. 2018). Research on PFAS has also demonstrated reduced

immune responses to vaccines in a community from the Faroe Islands (Grandjean et al. 2017). Therefore, the presence of pollutants in drinking water could be an issue even after a vaccine is discovered for COVID-19.

Studies on the ecological and environmental impact of the increased amount of plastic and other wastes being produced are certainly warranted, to evaluate risks to aquatic organisms and humans. Special attention to the respiratory issues associated to the use of cleaning (disinfectants) products is imperative, highlighting the need for stricter guidelines on their safety usage in both the healthcare environment and at home.

The selected persistent and toxic compounds and health effects discussed herein encompass only a small fraction of the endocrine disruptor contaminants possibly present in drinking water, as other pollutants, such as pesticides, herbicides, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbon (PAHs), and polybrominated diphenyl ethers (PBDE), as well as emerging contaminants, including pharmaceuticals, personal care products, disinfection by-products and metabolites, and transformation products, have also been implicated in immunotoxicity responses. Therefore, the health risks associated with the present of contaminants in drinking water, especially long-term exposures, are of paramount concern, and studies focusing on the effects of mixtures of these compounds are still lacking.

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