

Is There a Role for Environmental and Metabolic Factors Predisposing to Severe COVID-19?

Authors

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ABSTRACT

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic affects people around the world. However, there have been striking differences in the number of infected individuals and deaths in different countries. Particularly, within Central Europe in countries that are similar in ethnicity, age, and medical standards and have performed similar steps of containment, such differences in mortality rates remain inexplicable. We suggest to consider and explore environmental factors to explain these intriguing variations. Countries like Northern Italy, France, Spain, and UK have suffered from 5 times more deaths from the corona virus infection than neighboring countries like Germany, Switzerland, Austria, and Denmark related to the size of their respective populations. There is a striking correlation between the level of environmental pollutants including pesticides, dioxins, and air pollution such as NO₂ known to affect immune function and healthy metabolism with the rate of mortality in COVID-19 pandemic in these European countries. There is also a correlation with the use of chlorination of drinking water in these regions. In addition to the improvement of environmental protective programs, there are possibilities to lower the blood levels of these pollutants by therapeutic apheresis. Furthermore, therapeutic apheresis might be an effective method to improve metabolic inflammation, altered vascular perfusion, and neurodegeneration observed as long-term complications of COVID-19 disease.

Introduction

The 2020 pandemic of SARS-CoV-2 infection did not respect any borders and did not spare any regions of the world. Nevertheless, there are striking differences in the mortality rates and the occurrence of severe courses of the disease in different countries [1, 2]. This had been attributed to obvious differences of dissemination and efficiency of containment in different countries. It had also been related to the lack of knowledge of truly SARS-CoV-2 positive individuals versus the number of ill patients. Obviously, the availability and capacity to test for the virus are completely inconsistent between and sometimes even within different countries.

Finally, the different age profile, occurrence of comorbidities, quality of health care systems and even genetic predispositions have been blamed for the striking variations in the incidence of critical disease and lethal outcome [3–8].

Even if all these factors will play an important role they do not fully explain the reality of what we are seeing now.

Why did so many more casualties occur in Italy, France, Spain, the UK, and the United States than in other European countries like Germany, Austria, Switzerland or Scandinavia?

Even if methods of containment and exposure as well as infection rates play a crucial role, such drastic discrepancies remain currently inexplicable.

All these countries do have modern and efficient health care systems with more or less similar shortcomings. In all these countries, there are similar elderly populations with no major demographic differences. The same is true for the rate and distribution of comorbidities that had been defined as risk factors for severe COVID-19 disease such as diabetes, hypertension or heart disease [8–11]. There

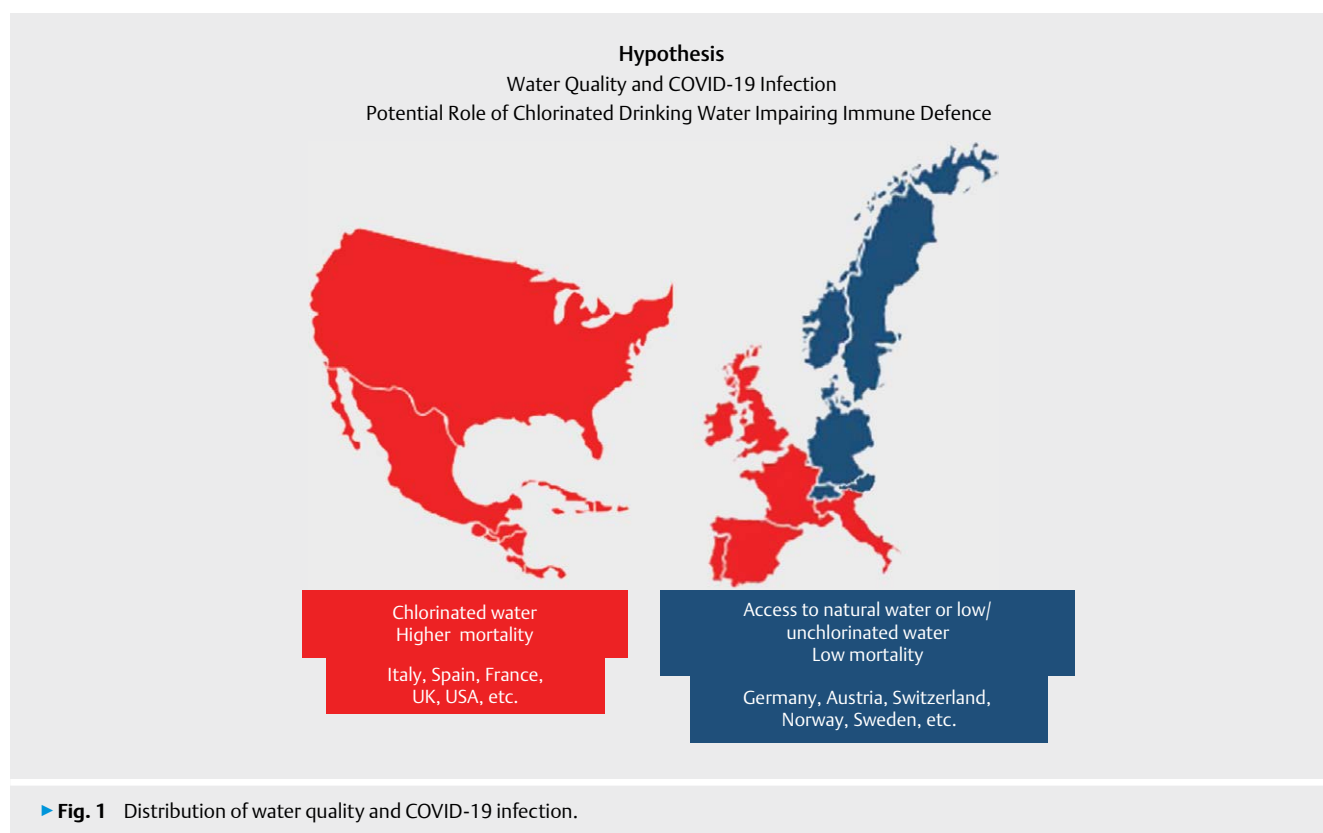
is currently no clear evidence for major differences in genetic predisposition between the populations of these Western countries.

Is There any Other Plausible Explanation?

Here we would like to open the discussion with a provocative hypothesis regarding these enigmatic differences in incidence of severe COVID-19 disease. We suggest that the use of chlorinated drinking water and/or other environmental pollutants could play a key role in the variation of susceptibility to the contraction of severe corona virus infection in these Western countries. Across Africa, South America, and Asia, tap water is unsuitable for drinking due to contamination and general hygienic conditions, which differ strongly from the Western world.

In contrast, in all countries of the Western world water can be used for drinking from the tap. However, there is one crucial difference. Whereas in countries like the US, UK, France, Spain, and Italy tap water is highly chlorinated, countries like Germany, Austria, Switzerland, and Scandinavia refrain from chlorination of their drinking water. In fact, we found an intriguing correlation of the rate of chlorination of tap water in different countries with the incidence of severity of COVID-19 disease (► Fig. 1).

Those countries that have not been exposing their populations to high levels of chlorinated water in the last decade exhibit a 2–20 fold lower death rate in the current pandemic. This is a most striking observation, which may be a mere coincidence but it should be worthwhile to seriously consider this conundrum.



Effects of Chlorinated Water on our Immune System

There is indeed ample and substantial evidence that chlorinated water may affect various functions of our immune system.

Chlorine gas is a formidable lung toxin [12]. Airway injury occurs due to oxidative damage, swarming of inflammatory cells, and resultant airway hyper-responsiveness [13]. Lipid peroxidation is a major damage event in the lung, and may critically affect the airway surface layer and its surfactant capacity [14, 15]. There is limited data regarding the availability of ingested or transdermally absorbed chlorine to partake in such processes.

When water is disinfected with chlorine and ingested, chlorinated, and brominated, mixed bromochloro acetates are formed [16]. Earlier studies in mice and rats exploring the potential of immunotoxicity of bromochloromethane and other disinfection by-products (DBPs) did not reveal any major effects on cellular or humoral immunity [17, 18]. Other research using experimental animals, however, reported a suppressive effect of chlorine-based drinking water on macrophage function [19, 20]. The intracellular redox status experiences depletion of reduced glutathione (GSH) [12]. The haloacetates, trichloroacetate, dichloroacetate, and their brominated analogues induce hepatic lipid peroxidation [16], and the liver is usually considered to be the target for lipid peroxidation processes related to chlorinated water [21]. The release of lipid toxins may be enhanced by SARS-CoV-2 driven liver disease [22], which is more prevalent in more severe systemic COVID-19 disease [23].

However, the small amounts of chlorine used for water disinfection, or evaporating from swimming pool surfaces may result in an attack of phospholipids by chlorine species, inducing chlorinated phospholipids. This consideration brings lipid peroxidation products into the center of attention [24]. Sodium chlorate (NaClO_3) is a by-product during disinfection of drinking water with chlorine dioxide. Human erythrocytes exhibit a significant increase in protein and lipid peroxidation, and a concomitant decrease in reduced glutathione [25, 26]. They offer an attractive shuttle system of peroxidized lipids, which come in indirect contact with the alveolar surface, as it is separated from the bloodstream by a membrane as thin as $0.2\ \mu\text{M}$. Chlorine driven ROS-induced lipid transformations without oxygen lead to formation 2-hexadecenal from sphingolipids. 2-Hexadecenal has a potent adverse biological potential. 2-Chloro-, and 2-bromo-substituted fatty aldehydes are produced by hypochlorous acid-induced endothelial damage, supposing a perfect storm at the lung-blood endothelial interface [27]. Whilst the exact pathways are still unknown it is plausible how ingested chlorine could via systemically released hepatic lipid peroxidation products, and by-products of lipid peroxidation in erythrocyte walls, be shuttled to the critical site of SARS-CoV-2 mediated disease: the alveolar ductal system and its neighboring endothelial surface [28–30].

More recent work has elucidated the role of polychloroaminated biphenyls on alterations of the innate immune response of marine mammals [31]. Interestingly, even swimming in a pool with chlorinated water induces an acute change of serum immune markers in humans [32]. Thus, in both males and females there was a significant decrease in cytokines following 40 min swimming in a chlorinated pool [32]. Likewise in the blood of children with a high content of organochlorine compounds in drinking water an imbalance

of cellular components of innate and adaptive immunity was found [33]. This suggests both acute and chronic effects of chlorinated water on the human innate immune response may interfere with the capacity of an individual to fight a virus infection.

Finally, chlorinated water may alter microbiome composition, the immune-gut barrier, and gene expression of intestinal cells [33]. Thus, numerous typical chlorinated disinfection by-products altered specifically genes in intestinal cells associated with immune and inflammation pathway. Therefore, these environmental aspects of the coronavirus pandemic need to be explored to develop better strategies and protection of our populations for the future.

Other Environmental Pollutants Impairing Immune Function

Beyond the role of chlorination in drinking water there may be other environmental pollutants playing a key role in causing a predisposition for viral infections such as by SARS-CoV-2. One of the most devastating chemical accidents occurred in 1976 in Northern Italy in Seveso, which also was an epicenter of the COVID-19 pandemic. The exposure of the population to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induced major medical problems including effects on the hormonal, metabolic, and immune systems. TCDD triggers a wide range of immunotoxic effects on both the humoral, cellular and also the innate immune response and interacts with the aryl hydrocarbon receptor [34–39]. It alters type 3 innate lymphoid cells in the colon and the entire intestinal tract [40, 41]. These effects on the immune system may even have been transferred to the next generation [42, 43]. Thus, offspring of pregnant rats exposed to TCDD exhibited an immunosuppression characterized by reduced thymus weight, reduced virus-associated natural killer (NK) cell, and specific antibody responses [42].

Furthermore, it has been shown that suppression of immune function led to an enhanced susceptibility to viral infections including influenza [44, 45]. In fact, even low levels of TCDD exposure lead to enhanced mortality to the influenza virus [45]. In addition to TCDD, exposure to pesticides may play an important role. Particularly, in Northern Italy more than 65 percent water samples from rivers and lakes exhibit high levels of pesticides including *p,p'*-DDE or *p,p'*-DDT and glyphosates.

These pesticides have been shown to exert a significant effect on the immune system. Persistent organic pollutants including 16 polychlorinated biphenyls and organochlorine factors increased pro-inflammatory cytokines, activated macrophages, and enhanced immunosenescence [46–48].

In experimental settings, glyphosate exposure may cause toxic effects on intestinal morphology, antioxidant capacity and barrier function [49].

PFAS, per- and polyfluorinated alkyl substances, are a huge class of non-classical persistent organic pollutants (POPs), which have been produced since the 1940s. Common use of these compounds, for example as surfactants, stain repellents, fire containment and many more applications has caused widespread environmental contamination. Human exposure occurs amongst other exposure pathways through air, water and particularly through terrestrial and aquatic food chains, including through food processing and packaging processes. Perfluorooctanesulfonic acid (PFOS) and perfluoro-

rooctanoic acid (PFOA) represent the two most frequently studied members of this large family of molecules. Although no geographical differences in the exposure to these chemicals can be deduced, they have to be discussed in the light of the COVID-19 pandemic.

In 2018, the European Food Safety Authority (EFSA) performed a risk assessment on PFOS and PFOA on human health. Although the risk assessment was primarily based on associations of the compounds to serum cholesterol levels, antibody response to vaccination in children was also identified as a critical effect [50]. This risk assessment is currently updated and the opinion is out for public consultation. In essence, it is confirmed for humans and animals, that levels of PFOS and PFOA are inversely linked to functionality of the immune system. The most significant concern regards the strong inverse association of PFAS blood levels and antibody response for example, following booster vaccinations to diphtheria and tetanus, particularly in children as shown on the Faroe Islands [51] and in Germany [52]. Supporting information from animal studies is available [53]. Perhaps more relevant to COVID-19 is a less pronounced inverse association with antibody titers [54].

Finally, important data link nitrogen dioxide (NO₂) levels to COVID-19 fatality rates [55]. Spatial analysis has been performed on a regional scale and combined with the number of death cases taken from 66 administrative regions in Italy, Spain, France, and Germany. Results show that out of the 4443 fatality cases, 3487 (78 %) were in five regions located in Northern Italy and central Spain. Interestingly, the same five regions exhibited the highest NO₂ concentrations combined with downwards airflow which prevents an efficient dispersion of air pollution. These results suggest that the long-term exposure to this pollutant may be an important contributor to fatality caused by the SARS-CoV-2 virus in these regions [55].

An explanation for susceptibility to progress to severe Covid disease may be provided by the observation that high levels of NO₂ affect innate immunity in the lung [56] and induce airway inflammation [57].

In summary, there is evidence that environmentally persistent compounds, particularly perfluorinated compounds and nitrogen dioxide, may compromise the immune response. Whilst no particular geographical association can be determined for perfluorinated compounds, regional segregation of death rates with NO₂ levels may provide more direct clues.

Effect of Environmental Pollutants on Lipid Levels and Cardiometabolism

All these environmental pollutants including dioxin-related chemicals as well as pesticides induce significant hormonal and metabolic alterations. Thus, exposure to DDT increases the incidence of diabetes in the NOD mouse model [58].

Acute dioxin exposure led to long-term metabolic consequences in mice [59]. Organochlorine pesticides may potentially mediate insulin resistance [60]. Population-based studies demonstrated an association between polychlorinated dibenzo-*p*-dioxin and polychlorinated biphenyls and the incidence of diabetes and hyperlipidemia [61]. Given the fact that diabetes, obesity and the metabolic syndrome are major risk factors for severe COVID-19 infections, the role of these environmental factors is even more

prominent. Of course, the risk of microbial contamination has to be balanced with the potential risk of disinfection by-products [62].

Environmental pollution has been correlated with severe dyslipidemia predisposing for metabolic syndrome and cardiovascular disease [63–65]. Organochlorine pesticides significantly aggravated disorders of fatty acid metabolism [66].

Similarly workers exposed to dioxin reportedly had elevated lipid levels [67]. Hyperlipidemia contributed to the higher role of atherosclerotic plaques and ischemic heart disease in these individuals [68].

Role of Lipids, Environmental Pollutants, and Therapeutic Apheresis

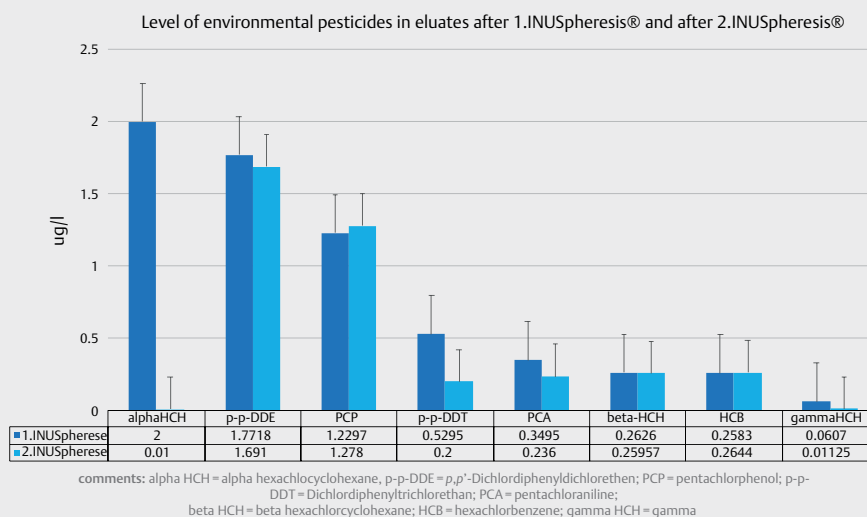
Changes in the lipid metabolism have been described in survivors of SARS-CoV infections [69]. Recovered SARS patients had increased phosphatidylinositol and lysophosphatidylinositol levels after 12 years, which might be also a result of treatment with high doses of methylprednisolone. Therefore, long-term effects of therapeutic interventions on the lipid metabolism should be considered in COVID-19 patients.

The impact of the lipoprotein metabolism on the clinical outcome in COVID-19 patients is currently not well understood. Recently, the impact of underlying cardiovascular disease (CVD) and myocardial injury on fatal outcomes in patients with COVID-19 has been described [70–72]. This study compared 52 patients with and 135 patients without elevation of troponin T (TnT) levels. Total, high-density lipoprotein, and low-density lipoprotein (LDL) cholesterol levels did not differ between both groups, but patients with elevated TnT levels had higher triglyceride levels. The inflammatory biomarkers high-sensitivity C-reactive protein and procalcitonin were significantly increased in patients with elevated TnT levels.

Other strategies to lower lipoprotein levels might represent interesting novel therapeutic approaches. In general, lowering LDL cholesterol and lipoprotein(a) levels could have beneficial effects like upregulation of ACE2 and prevention of cardiovascular complications during COVID-19 infection. Lipoprotein apheresis could be an attractive alternative therapeutic approach to treat critically ill patients. Apheresis has been shown to mediate lipid-lowering and anti-inflammatory effects [73]. This might mediate beneficial effects in COVID-19 patients with elevated CRP levels and inflammation.

Therefore, lipoprotein apheresis using rigidly implemented isolation measures might be a novel protective strategy in the treatment of COVID-19 patients. The European Group – International Society for Apheresis e.V. (E-ISA) – has recently joined the German Center for Infection Research, the ESCMID Emerging Infections Task Force and a number of other institutions including the Robert Koch Institute in the LEOSS (Lean European Open Survey on SRAS-CoV-s Infected Patients) registry. This is an open, international and anonymous registry covering all aspects of COVID-19 infections from diagnosis, laboratory measurements over medical treatments to clinical outcomes (<https://leoss.net>). This initiative will help defining the impact of apheresis therapy on COVID-19 patients.

Furthermore, therapeutic apheresis is an efficient biophysical method to remove metabolic inflammatory immunological and environmental components from the blood of patients. Many patients with severe COVID-19 infection exhibit lymphopaenia which



► **Fig. 2** Level of environmental pesticides before and after therapeutic apheresis (INUSpheres®).

may lead to secretion of high amounts of inflammatory cytokines and cytokine storm [74–76].

Specifically therapeutic environmental apheresis (INUSpheres®) may be useful. We have previously shown that this method allows an effective removal of lipoproteins, inflammatory cytokines as well as environmental pollutants. This includes a reduction of heavy metals, but also a reduction of environmental pesticides (► **Fig. 2**). Environmental apheresis® is therefore useful to improve parameters of metabolic inflammation and hyperlipidemia, which have been shown to be major risk factors for the development of severe Coronavirus disease 2019. Furthermore, it has been shown to improve neuroinflammation and polyneuropathy [73, 77]. Thus, the removal and reduction of environmental pollutants together with the reduction of lipids and inflammatory factors may provide a protective mechanism for prevention and mitigation of severe corona virus infections.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] Ioannidis JPA. Coronavirus disease 2019: The harms of exaggerated information and non-evidence-based measures. *Eur J Clin Invest* 2020; doi:10.1111/eci.13223: e13223
- [2] Boccia S, Ricciardi W, Ioannidis JPA. What other countries can learn from Italy during the COVID-19 pandemic. *JAMA Intern Med* 2020; doi:10.1001/jamainternmed.2020.1447
- [3] Bedford J, Enria D, Giesecke J et al. COVID-19: Towards controlling of a pandemic. *Lancet* 2020; 395: 1015–1018
- [4] Koo JR, Cook AR, Park M et al. Interventions to mitigate early spread of SARS-CoV-2 in Singapore: A modelling study. *Lancet Infect Dis* 2020; doi:10.1016/S1473-3099(20)30162-6
- [5] Prem K, Liu Y, Russell TW et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: A modelling study. *Lancet Public Health* 2020; 5: e261–e270
- [6] Sorbello M, El-Boghdady K, Di Giacinto I et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia* 2020; 75: 724–732
- [7] Kinross P, Suetens C, Gomes Dias J et al. Rapidly increasing cumulative incidence of coronavirus disease (COVID-19) in the European Union/ European Economic Area and the United Kingdom, 1 January to 15 March 2020. *Euro Surveill* 2020; 25: doi:10.2807/1560-7917.ES.2020.25.11.2000285
- [8] Bornstein SR, Dalan R, Hopkins D et al. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol* 2020; 16: 297–298
- [9] Bornstein SR, Rubino F, Khunti K et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; doi:10.1016/S2213-8587(20)30152-2
- [10] Dalan R, Bornstein SR, El-Armouche A et al. The ACE-2 in COVID-19: Foe or Friend? *Horm Metab Res* 2020; 52: 257–263
- [11] Steenblock C, Todorov V, Kanczkowski W et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the neuroendocrine stress axis. *Mol Psychiatry* 2020; doi:10.1038/s41380-020-0758-9
- [12] Russell D, Blain PG, Rice P. Clinical management of casualties exposed to lung damaging agents: a critical review. *Emerg Med J* 2006; 23: 421–424

- [13] McGovern TK, Powell WS, Day BJ et al. Dimethylthiourea protects against chlorine induced changes in airway function in a murine model of irritant induced asthma. *Respir Res* 2010; 11: 138
- [14] Batenburg JJ. Surfactant phospholipids: Synthesis and storage. *Am J Physiol* 1992; 262: L367–L385
- [15] Zarogiannis SG, Jurkuvenaite A, Fernandez S et al. Ascorbate and deferoxamine administration after chlorine exposure decrease mortality and lung injury in mice. *Am J Respir Cell Mol Biol* 2011; 45: 386–392
- [16] Austin EW, Parrish JM, Kinder DH et al. Lipid peroxidation and formation of 8-hydroxydeoxyguanosine from acute doses of halogenated acetic acids. *Fundam Appl Toxicol* 1996; 31: 77–82
- [17] French AS, Copeland CB, Andrews D et al. Evaluation of the potential immunotoxicity of bromodichloromethane in rats and mice. *J Toxicol Environ Health A* 1999; 56: 297–310
- [18] French AS, Copeland CB, Andrews DL et al. Evaluation of the potential immunotoxicity of chlorinated drinking water in mice. *Toxicology* 1998; 125: 53–58
- [19] Exon JH, Koller LD, O'Reilly CA et al. Immunotoxicologic evaluation of chlorine-based drinking water disinfectants, sodium hypochlorite and monochloramine. *Toxicology* 1987; 44: 257–269
- [20] Shopp GM Jr., Sanders VM, White KL et al. Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene. *Drug Chem Toxicol* 1985; 8: 393–407
- [21] Lu WQ, Chen XN, Yue F et al. Studies on the in vivo and in vitro mutagenicity and the lipid peroxidation of chlorinated surface (drinking) water in rats and metabolically competent human cells. *Mutat Res* 2002; 513: 151–157
- [22] Xu L, Liu J, Lu M et al. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; 40: 998–1004
- [23] Parohan M, Yaghoubi S, Seraj A. Liver injury is associated with severe Coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. *Hepatol Res* 2020, doi:10.1111/hepr.13510
- [24] Reis A, Spickett CM. Chemistry of phospholipid oxidation. *Biochim Biophys Acta* 2012; 1818: 2374–2387
- [25] Ali SN, Ahmad MK, Mahmood R. Sodium chlorate, a herbicide and major water disinfectant byproduct, generates reactive oxygen species and induces oxidative damage in human erythrocytes. *Environ Sci Pollut Res Int* 2017; 24: 1898–1909
- [26] Ali SN, Mahmood R. Sodium chlorite increases production of reactive oxygen species that impair the antioxidant system and cause morphological changes in human erythrocytes. *Environ Toxicol* 2017; 32: 1343–1353
- [27] Ebenezer DL, Fu P, Ramchandran R et al. S1P and plasmalogen derived fatty aldehydes in cellular signaling and functions. *Biochim Biophys Acta Mol Cell Biol Lipids* 2020; 1865: 158681
- [28] Sun X, Wang T, Cai D et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev* 2020, doi:10.1016/j.cytogfr.2020.04.002
- [29] Geng YJ, Wei ZY, Qian HY et al. Pathophysiological characteristics and therapeutic approaches for pulmonary injury and cardiovascular complications of coronavirus disease 2019. *Cardiovasc Pathol* 2020; 47: 107228
- [30] Salome B, Magen A. Dysregulation of lung myeloid cells in COVID-19. *Nat Rev Immunol* 2020; 20: 277
- [31] Desforges JP, Sonne C, Levin M et al. Immunotoxic effects of environmental pollutants in marine mammals. *Environ Int* 2016; 86: 126–139
- [32] Vlaanderen J, van Veldhoven K, Font-Ribera L et al. Acute changes in serum immune markers due to swimming in a chlorinated pool. *Environ Int* 2017; 105: 1–11
- [33] Lanin DV, Zaytseva NV, Zamlyanova MA et al. Characteristics of regulatory system in children exposed to the environmental chemical factors. *Gig Sanit* 2014; 23–26
- [34] Trikha P, Lee DA. The role of AhR in transcriptional regulation of immune cell development and function. *Biochim Biophys Acta Rev Cancer* 2020; 1873: 188335
- [35] Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol* 2019; 19: 184–197
- [36] Koch CA. How Can Environmental Factors Contribute to the Incidence of Thyroid Cancer? *Horm Metab Res* 2017; 49: 229–231
- [37] Pang C, Zhu C, Zhang Y et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin affects the differentiation of CD4 helper T cell. *Toxicol Lett* 2019; 311: 49–57
- [38] Feng Y, Tian J, Krylova I et al. Chronic TCDD exposure results in the dysregulation of gene expression in splenic B-lymphocytes and in the impairments in T-cell and B-cell differentiation in mouse model. *J Environ Sci (China)* 2016; 39: 218–227
- [39] North CM, Crawford RB, Lu H et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin-mediated suppression of toll-like receptor stimulated B-lymphocyte activation and initiation of plasmacytic differentiation. *Toxicol Sci* 2010; 116: 99–112
- [40] Li Y, Xie HQ, Zhang W et al. Type 3 innate lymphoid cells are altered in colons of C57BL/6 mice with dioxin exposure. *Sci Total Environ* 2019; 662: 639–645
- [41] Cervantes-Barragan L, Colonna M. Chemical sensing in development and function of intestinal lymphocytes. *Curr Opin Immunol* 2018; 50: 112–116
- [42] Ross PS, de Swart RL, van der Vliet H et al. Impaired cellular immune response in rats exposed perinatally to Baltic Sea herring oil or 2,3,7,8-TCDD. *Arch Toxicol* 1997; 71: 563–574
- [43] Holsapple MP, Snyder NK, Wood SC et al. A review of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced changes in immunocompetence: 1991 update. *Toxicology* 1991; 69: 219–255
- [44] Yang YG, Lebec H, Burleson GR. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on pulmonary influenza virus titer and natural killer (NK) activity in rats. *Fundam Appl Toxicol* 1994; 23: 125–131
- [45] Burleson GR, Lebec H, Yang YG et al. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on influenza virus host resistance in mice. *Fundam Appl Toxicol* 1996; 29: 40–47
- [46] Kumar J, Lind PM, Salihovic S et al. Influence of persistent organic pollutants on the complement system in a population-based human sample. *Environ Int* 2014; 71: 94–100
- [47] Weis GCC, Assmann CE, Cadona FC et al. Immunomodulatory effect of mancozeb, chlorothalonil, and thiophanate methyl pesticides on macrophage cells. *Ecotoxicol Environ Saf* 2019; 182: 109420
- [48] Ryu DH, Yu HT, Kim SA et al. Is chronic exposure to low-dose organochlorine pesticides a new risk factor of T-cell immunosenescence? *Cancer Epidemiol Biomarkers Prev* 2018; 27: 1159–1167
- [49] Qiu S, Fu H, Zhou R et al. Toxic effects of glyphosate on intestinal morphology, antioxidant capacity and barrier function in weaned piglets. *Ecotoxicol Environ Saf* 2020; 187: 109846
- [50] Knutsen HK, Alexander J, Barregård L et al. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA Journal* 2018; 16: 5333
- [51] Grandjean P, Andersen EW, Budtz-Jorgensen E et al. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA* 2012; 307: 391–397
- [52] Abraham K, Mielke H, Fromme H et al. Internal exposure to perfluoroalkyl substances (PFASs) and biological markers in 101 healthy 1-year-old children: Associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. *Arch Toxicol* 2020, doi:10.1007/s00204-020-02715-4

- [53] Looker C, Luster MI, Calafat AM et al. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicol Sci* 2014; 138: 76–88
- [54] Peden-Adams MM, Keller JM, Eudaly JG, Berger J et al. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicol Sci* 2008; 104: 144–154
- [55] Ogen Y. Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ* 2020; 726: 138605
- [56] Estrella B, Naumova EN, Cepeda M et al. Effects of air pollution on lung innate lymphoid cells: Review of in vitro and in vivo experimental studies. *Int J Environ Res Public Health* 2019; 16: pii: E2347. doi:10.3390/ijerph16132347
- [57] Ji X, Han M, Yun Y et al. Acute nitrogen dioxide (NO₂) exposure enhances airway inflammation via modulating Th1/Th2 differentiation and activating JAK-STAT pathway. *Chemosphere* 2015; 120: 722–728
- [58] Cetkovic-Cvrlje M, Olson M, Schindler B et al. Exposure to DDT metabolite p,p'-DDE increases autoimmune type 1 diabetes incidence in NOD mouse model. *J Immunotoxicol* 2016; 13: 108–118
- [59] Hoyeck MP, Blair H, Ibrahim M et al. Long-term metabolic consequences of acute dioxin exposure differ between male and female mice. *Sci Rep* 2020; 10: 1448
- [60] Kim YA, Park JB, Woo MS et al. Persistent organic pollutant-mediated insulin resistance. *Int J Environ Res Public Health* 2019; 16: pii: E448. doi:10.3390/ijerph16030448
- [61] Huang CY, Wu CL, Yang YC et al. Association between dioxin and diabetes mellitus in an endemic area of exposure in Taiwan: A population-based study. *Medicine (Baltimore)* 2015; 94: e1730
- [62] Arisawa K. Recent decreasing trends of exposure to PCDDs/PCDFs/dioxin-like PCBs in general populations, and associations with diabetes, metabolic syndrome, and gout/hyperuricemia. *J Med Invest* 2018; 65: 151–161
- [63] Koch CA, Diamanti-Kandarakis E. Introduction to endocrine disrupting chemicals—is it time to act? *Rev Endocr Metab Disord* 2015; 16: 269–270
- [64] Mao S, Chen G, Liu F et al. Long-term effects of ambient air pollutants to blood lipids and dyslipidemias in a Chinese rural population. *Environ Pollut* 2020; 256: 113403
- [65] Jin C, Zeng Z, Wang C et al. Insights into a possible mechanism underlying the connection of carbendazim-induced lipid metabolism disorder and gut microbiota dysbiosis in mice. *Toxicol Sci* 2018; 166: 382–393
- [66] Liu Q, Wang Q, Xu C et al. Organochloride pesticides impaired mitochondrial function in hepatocytes and aggravated disorders of fatty acid metabolism. *Sci Rep* 2017; 7: 46339
- [67] Crow KD. Lipid profiles in dioxin-exposed workers. *Lancet* 1979; 1: 982
- [68] Pelclova D, Fenclova Z, Preiss J et al. Lipid metabolism and neuro-psychological follow-up study of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Int Arch Occup Environ Health* 2002; 75: (Suppl) S60–S66
- [69] Wu Q, Zhou L, Sun X et al. Altered lipid metabolism in recovered sars patients twelve years after infection. *Sci Rep* 2017; 7: 9110
- [70] Guo T, Fan Y, Chen M et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020, doi: 10.1001/jamacardio.2020.1017
- [71] Kaur N, Starling AP, Calafat AM et al. Longitudinal association of biomarkers of pesticide exposure with cardiovascular disease risk factors in youth with diabetes. *Environ Res* 2020; 181: 108916
- [72] Ashbolt NJ. Risk analysis of drinking water microbial contamination versus disinfection by-products (DBPs). *Toxicology* 2004; 198: 255–262
- [73] Bornstein SR, Voit-Bak K, Rosenthal P et al. Extracorporeal apheresis therapy for Alzheimer disease-targeting lipids, stress, and inflammation. *Mol Psychiatry* 2020; 25: 275–282
- [74] Palm NW, Medzhitov R. Not so fast: Adaptive suppression of innate immunity. *Nat Med* 2007; 13: 1142–1144
- [75] Liu J, Li S, Liu J et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine* 2020; 55: 102763
- [76] Lin JH, Chen YC, Lu CL et al. Application of plasma exchange in association with higher dose CVVH in cytokine storm complicating COVID-19. *J Formos Med Assoc* 2020, doi:10.1016/j.jfma.2020.04.023
- [77] Straube R, Muller G, Voit-Bak K et al. Metabolic and non-metabolic peripheral neuropathy: Is there a place for therapeutic apheresis? *Horm Metab Res* 2019; 51: 779–784