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Short communication

Disinfectant-induced hormesis: An unknown environmental threat of the application of disinfectants to prevent SARS-CoV-2 infection during the COVID-19 pandemic?

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ABSTRACT

Massive additional quantities of disinfectants have been applied during the COVID-19 pandemic as infection preventive and control measures. While the application of disinfectants plays a key role in preventing the spread of SARS-CoV-2 infection, the effects of disinfectants applied during the ongoing pandemic on non-target organisms remain unknown. Here we collated evidence from multiple studies showing that chemicals used for major disinfectant products can induce hormesis in various organisms, such as plants, animal cells, and microorganisms, when applied singly or in mixtures, suggesting potential ecological risks at sub-threshold doses that are normally considered safe. Among other effects, sub-threshold doses of disinfectant chemicals can enhance the proliferation and pathogenicity of pathogenic microbes, enhancing the development and spread of drug resistance. We opine that hormesis should be considered when evaluating the effects and risks of such disinfectants, especially since the linear-no-threshold (LNT) and threshold dose-response models cannot identify or predict their effects.

1. Introduction

The world is currently facing the fifth pandemic after the 1918 flu pandemic, which is caused by the novel coronavirus disease 2019 (COVID-19) (Liu et al., 2020; Neagu et al., 2021). The first symptom onset might have occurred on 1 December 2019, and while the press initially called the disease Wuhan pneumonia, whole-genome sequencing revealed that a novel coronavirus was responsible for the disease (Liu et al., 2020). The World Health Organization (WHO) named the virus '2019 novel coronavirus' (2019-nCoV) in mid January 2020, following by its official declaration as 'coronavirus disease 2019' (COVID-19) one month later (Liu et al., 2020). Some weeks later, the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) finally recognized the virus as "forming a sister clade to the prototype human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species *Severe acute respiratory syndrome-related coronavirus*", designated as 'SARS-CoV-2' (CSG-ICTV, 2020). As of 5 October 2021, 236,193,324 cases of infection, 213,255,597 recoveries, and 4,823,425 deaths have been recorded across the globe (https://www.worldometers.info/coronavirus/; last updated: 5 October 2021, 06:50 GMT).

To prevent further spreading of SARS-CoV-2, governments all over the world imposed mobility restriction measures of various degrees of severity, including local, regional, or national lockdowns (Benchrif et al., 2021; Calina et al., 2021; Deroubaix et al., 2021; Kim et al., 2021; Marinello et al., 2021), and mandated the application of public health-based measures such as wearing masks and sanitizing public spaces (Dadras et al., 2021; Subpiramaniyam, 2021). Strategies to halt the infection cycle have included the disinfection of objects and surfaces (Barcelo, 2020; Khan and Yadav, 2020; Kwok et al., 2021). As a direct consequence of this strategy and its widespread implementation, disinfectants have been massively applied across the globe, and the extent of

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this practice is considerable. For example, disinfectants should be applied multiple times per day in contaminated sites, with each treatment lasting enough time per application (e.g. at least 30 min for 2000 mg/L chlorine-containing disinfectants) (Barcelo, 2020), while China had dispensed 2000–5000 tons of disinfectants in Wuhan alone (Zhang et al., 2020). The effectiveness of the disinfectants to inactivate SARS-CoV-2 depends on various factors, however, many studies show that such chemical products are efficient in inactivating the virus if applied properly (Dhama et al., 2021; Sharafi et al., 2021; Shimabukuro et al., 2020).

While the effectiveness to reduce significantly the spread of SARS-CoV-2 is an area of scientific research, there are potential side effects on the environment, affecting various creatures such as plants, insects, and wild animals (Dhama et al., 2021; Ghafoor et al., 2021). Several studies examine in detail the potential impacts of the application of such disinfectants to the environment (Ankit et al., 2021; Bonin et al., 2020; Chen et al., 2021; Dhama et al., 2021; Nabi et al., 2020; Zhang et al., 2020). There is, however, no study evaluating the effects of such chemicals within the context of dose-response relationship and whether such chemicals can induce hormesis in various living organisms, despite the high importance of this for risk assessment considerations (Agathokleous and Calabrese, 2020a). Here, we aimed at examining the published literature for evidence supporting the occurrence of hormesis as a result of exposure to compounds used in disinfectants applied to surfaces, as well as ethanol-based compounds used as preventive measures against SARS-CoV-2 infection. Because disinfectants applied to surfaces include many chemicals other than ethanol that are longer-lived and thus expected to have wider environmental consequences, we focused on the potential implications of hormesis induced by surface disinfectants. The herein analysis suggests that the massive application of disinfectants for containing SARS-CoV-2 may be a double-edged sword, inhibiting/preventing the virus but also imposing some potentially significant but non-apparent costs or risks by affecting other non-target organisms in a dose-dependent manner, and finally promoting traits of drug resistance.

2. Presentation of the analysis and concerns

The massive release of SARS-CoV-2 disinfectants into the waste (water) systems and run-off continuously since early 2020 is alarming in terms of potential effects on non-target species (other than SARS-CoV-2) (Subpiramaniyam, 2021). Collectively, the WHO considered the application of chlorine-based chemicals for disinfecting health-care settings and other environmental surfaces (WHO, 2020). Moreover, the US Environmental Protection Agency (EPA) is continuously updating the disinfectants list for application onto surfaces (acknowledged also by WHO (2020)), including various chemicals, such as H_2O_2 alone or with peroxyacetic acid (peracetic acid), dodecylbenzenesulfonic acid alone or with L-lactic acid, quaternary ammonium alone or with isopropanol (isopropyl alcohol), and sodium carbonate peroxyhydrate with tetraacetyl ethylenediamine (https://cfpub.epa.gov/wizards/disinfectants; Accessed on 3 August 2021). A large proportion of the EPA's recommended disinfectant products for application against SARS-CoV-2 is based on quaternary ammonium compounds (QACs) (Hora et al., 2020). Although QACs were extensively applied and detected in sediments, surface waters, and wastewater before the current pandemic, their use has increased during the SARS-CoV-2 pandemic, which is of more concern due to their role into antibiotic resistance (Hora et al., 2020; Zhang et al., 2015).[1] Additional disinfectants that can be applied to halt SARS-CoV spread are chemicals such as ethanol (Dhama et al., 2021; Hirose et al., 2020; Ijaz et al., 2021; Kwok et al., 2021; Rabenau et al., 2005; Xiling et al., 2021).

Massive application of disinfectants against COVID-19, however, can have various negative effects on humans and the environment, poses potential environmental/ecological risks, especially in urban ecosystems, and may undermine the concept of 'One Health' (Nabi et al., 2020). For example, disinfectants can affect the mucosal lining, thus leading to inflammation, irritation, swelling, and ulceration of the respiratory tract (Dhama et al., 2021). They can also cause skin dryness and heighten the risk of developing asthma, chronic obstructive pulmonary disease, and impaired brain development, and infertility in children (Dhama et al., 2021). In addition to the effects on humans, a large discharge of disinfectants into lakes, rivers, sewage, due to activities including the cleaning of external floors, markets, and streets (Subpiramaniyam, 2021), and disinfection of wastewater derived from heavy activities, such as healthcare facilities, hotels, and factories, can affect living organisms (Dhama et al., 2021). For example, chlorine-based disinfectants may (i) oxidize proteins and destruct cell walls of aquatic wildlife and plants, (ii) generate byproducts, e.g. haloacetic acids and trihalomethanes, which may be highly toxic to aquatic flora and fauna, (iii) bond with other contaminants and transform into harmful compounds, and (iv) potentially affecting the activity of pollutant-removing microorganisms in wastewater treatment plants (Dhama et al., 2021; Sedlak and Von Gunten, 2011; Subpiramaniyam, 2021; Zhang et al., 2020). In the worst case scenario, animals may even die due to overload of disinfectants, as it has been reported after application of massive amounts of disinfectants to a coronavirus epicenter (Nabi et al., 2020). Therefore, the ongoing massive application of disinfectants may threaten numerous creatures in terrestrial and aquatic systems (Zhang et al., 2020), urging for evaluations of dose-response relationships in a plethora of living organisms exposed to disinfectants.

Although the effects of such disinfectants to non-target organisms remain unknown, there is evidence that such chemicals can induce hormesis with significant responses at sub-threshold doses, i.e. at doses smaller than the traditional toxicological threshold (Fig. 1). Examples of such chemicals shown to induce hormesis include chlorine-based chemicals (Zhang et al., 2008), H_2O_2 (Huang et al., 2019; Ludovico and Burhans, 2014; Semchyshyn, 2014; Semchyshyn and Valishkevych, 2016), various QACs (Hrubec et al., 2021; Li et al., 2019; Mo et al., 2020), and ethanol (Calabrese and Baldwin, 2003; Kar et al., 2021; Semchyshyn, 2014). These chemicals are used for both hand and surface sanitizer products and are among the most widely applied disinfectants during the current pandemic (Dhama et al., 2021; Jing et al., 2020; World Health Organization (WHO), 2020). Importantly, hormesis was induced by not only single chemicals but also mixtures, specifically in studies with QACs, which can display also additive or synergistic effects (Mo et al., 2020); hormetic effects of complex mixtures of chemicals have also been reported by numerous other studies (Docea et al., 2019; Tsatsakis et al., 2019). Extensive experimentation with yeast subjected to a series of dilutions of numerous disinfectants revealed that most of the disinfectants induced toxicity followed by an overcompensation stimulation (Branham, 1929). The occurrence of overcompensation stimulation within a hormetic framework is very common, and highly generalizable (Calabrese, 2001). These findings suggest that both direct stimulation and overcompensation can occur in the framework of disinfectant-induced hormesis, which would make the concern greater due to the complexity to identify and predict such effects. Newer studies incorporating a time component would be needed to examine disinfectant-induced time-dependent hormesis in different organisms and endpoints.

The preceding collated evidence indicates the induction of hormesis by various disinfectants. Hormesis has also been widely observed in various living organisms exposed to numerous other pollutants and contaminants of emerging concern of aquatic and terrestrial systems, including active pharmaceutical ingredients, formaldehyde, fungicides, heavy metals and other elements, herbicides, hydrocarbons, microplastics, nanomaterials, and ozone (Agathokleous et al., 2021c;

[1] See also the information provided by the US EPA at https://www.epa.gov/coronavirus/disinfectant-use-and-coronavirus-covid-19.

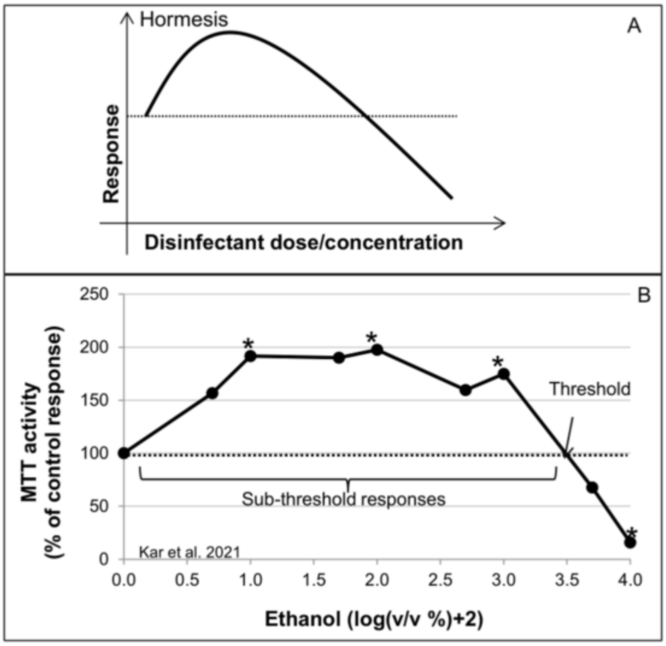

Fig. 1. A: A schematic representation of hormetic dose-response relationship. Similar hormetic-like responses were found in various organisms exposed to different types of disinfectant-containing chemicals. **B**: An example of hormetic dose-response relationship. Cell viability assay was evaluated with the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay in a mouse embryonic fibroblast cell line. The figure has been created based on data reported by Kar et al. (2021), and asterisk above a mean indicates significant difference from the control based on the original authors' statistical analyses. The ethanol concentrations were transformed for presentation purposes. The original concentrations were 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, and 10 v/v % for 48 h. Data were extracted from the relevant figure of the published article using Adobe Photoshop CS4 Extended v.11 (Adobe Systems Incorporated, CA, USA).

Agathokleous and Calabrese, 2020b, 2021; Belz and Duke, 2017; Calabrese and Agathokleous, 2021; Carvalho et al., 2020; Erofeeva, 2021a, 2021b; Iavicoli et al., 2021; Shahid et al., 2020). The induction of hormesis by so many contaminants with considerably differed molecular structure suggests the possibility that any chemical agent may induce hormesis when applied at the right doses. Nevertheless, more studies are needed to (i) examine whether all the disinfectants that are currently available and applied induce hormesis in various creatures, (ii) reveal what the underlying mechanisms are, and (iii) understand whether the underlying mechanisms and quantitative traits of hormetic responses differ among disinfectants.

Hormesis was induced in various organisms, such as freshwater luminescent bacteria (*Vibrio qinghaiensis* sp. Q67) (Mo et al., 2020), hydroponically-cultivated higher plants (*Triticum aestivum* L.) (Li et al., 2019), human neuroblastoma cell line (Huang et al., 2019), humans (associational) (Hrubec et al., 2021), mouse embryonic fibroblast cells (Kar et al., 2021), mouse macrophages (Zhang et al., 2008), and yeast (*Saccharomyces cerevisiae* Meyen *ex* E.C. Hansen) (Semchyshyn, 2014; Semchyshyn and Valishkevych, 2016). These recent findings extend older findings of ethanol- and other disinfectant-induced hormesis in different kinds of cells and experimental models (Branham, 1929; Calabrese and Baldwin, 2003), and the magnitude of the sub-threshold effects is commonly within two-fold of the control response/status, in agreement with the broad hormesis literature for numerous stresses, organisms, and endpoints (Agathokleous et al., 2020; Calabrese et al., 2019; Calabrese and Agathokleous, 2021; Sun et al., 2021). Hormetic responses have been reported for a plethora of endpoints, such as cell viability (Zhang et al., 2008) and proliferation [MTT activity (Kar et al., 2021)], cyanobacteria luciferase (Mo et al., 2020), plant shoot and root biomass (Li et al., 2019), human health-related biomarkers (Hrubec et al., 2021), and levels of reduced glutathione (GSH) and gene expression of GCLC and NQO-1 (Zhang et al., 2008). H_2O_2 also promoted PAC1-R promoter activity in a dose-dependent fashion, which was inhibited by the transcription factor specificity protein 1 (SP1) inhibitor mithramycin A (Huang et al., 2019), while yeast colony growth positively correlated with the glutathione reductase activity (Semchyshyn, 2014; Semchyshyn and Valishkevych, 2016). Not only can cells show adaptability to sub-threshold doses of ethanol (Kar et al., 2021), but also H_2O_2 applied at sub-threshold doses could lead to cross-resistance of budding yeast (*S. cerevisiae*) to different stresses, a phenomenon where the regulatory protein Yap1 plays an important role (Semchyshyn, 2014). Although hormetic effects depend on the carbohydrate (energy source) in growth medium (Semchyshyn and Valishkevych, 2016), these findings suggest that low doses of disinfectants in the environment may change the sensitivity of non-target organisms to different environmental stresses.

These results also suggest that sub-threshold doses of disinfectants can have various biologically positive effects on non-target organisms, like many other contaminants (Agathokleous et al., 2021c, 2020; Calabrese and Agathokleous, 2021; Iavicoli et al., 2021); however, with the potential to translate to ecologically/environmentally negative outcomes. For example, while they enhance plant biomass, they can stimulate emerging fungal pathogens (Pérez-Torrado and Querol, 2016) and perplex their control in specific environmental settings, especially if such sub-threshold responses are linked with mechanisms involved in the development of resistance (Iavicoli et al., 2021). Bacterial populations exhibit high heterogeneity and are composed of cells of various ages and physiological states, while antibiotics effects on bacteria might be defined by how many molecules effectively interact with individual cells (Baquero and Levin, 2020). Of increased concern is that there is ample evidence indicating that QACs can (i) lead to proliferation of pathogenic, multidrug-resistant bacteria and cross-resistance of bacteria to antibiotics, (ii) emergence of microflora enriched with bacterial strains presenting resistance to clinically important antimicrobial agents, and (iii) promotion of the fixation of novel genetic elements, which assist in spreading resistance genes (Akimitsu et al., 1999; Braoudaki and Hilton, 2004; Buffet-Bataillon et al., 2012; Chen et al., 2021; Hora et al., 2020; Pereira and Tagkopoulos, 2019; Tezel and Pavlostathis, 2011; Zhang et al., 2015). These may add to the existing issue of the increase in multidrug-resistant organisms (Exner et al., 2020; see also Berendonk et al., 2015). Even if some disinfectants such as ethanol may not lead to environmental consequences, it is still possible that bacterial resistance may develop in the bacterial flora associated with the skin of humans and other animals (Chan, 1999; Chen et al., 2021; Ghafoor et al., 2021; Schwarz et al., 2017), a hypothesis that remains to be studied.

It should also be mentioned, however, that different disinfectants may have distinct extent of spatiotemporal impact of the longer-lived compounds, such as QACs, versus the shorter-lived chemicals, such as H_2O_2 and ethanol (Dhama et al., 2021). The reduced longevity of H_2O_2 and ethanol, e.g. due to its sensitivity to light or its high vapor pressure, may be expected to limit the consequences to local environments and skin (hence people), whilst the longer-lived compounds may be expected to have wider-reaching environmental effects (ecosystems). Importantly, there is a wealth of studies illustrating that exposure of various creatures to low doses, which are smaller than the traditional toxicological threshold, can have long-lasting effects, even transmitted transgenerationally and observed even more than ten generations later (Agathokleous et al., 2021b; Agathokleous and Calabrese, 2020b; Calabrese and Agathokleous, 2020). These suggest that effects of massively applied disinfectants might persist for a long time in the environment, indicating a need for new-generation (eco)toxicological studies that would be directed to reveal potential transgenerational effects of sub-toxic doses of disinfectants. Therefore, hormesis should be considered in risk assessment because the traditional and biologically irrelevant threshold and linear-no-threshold (LNT) dose response models cannot capture effects that occur in the hormetic (low-dose) zone (Agathokleous et al., 2021a, 2019; Agathokleous and Calabrese, 2020a; Tsatsakis, 2021). No consideration of hormetic responses may lead to considerably incorrect estimates of points of departure, while the complexity of disinfectant and other chemical mixtures and the non-linear hormetic responses would make the derivation of reliable permissible levels challenging for risk assessment-based regulation (Agathokleous et al., 2021d; Tsatsakis, 2021).

Disinfectants are also widely used for drinking water treatment (Humans, 1991; Pichel et al., 2019; Tsitsifli and Kanakoudis, 2018), especially in the US, South Europe, and China. Hence, in several countries chlorination takes place in the drinking water plant and at the effluent to ensure that the drinking water network is charged with enough chlorine when reaching the public. The recent massive documentation of hormetic responses induced by disinfectants and other chemicals suggests the possibility that sub-toxic doses of such chemicals in the tap water might have unknown effects that traditional dose-response models fail to identify. Therefore, new generation studies are needed to evaluate for potential effects of disinfectants added into the tap water at doses that are smaller than the traditional toxicological threshold. A complementary tool for assessing the whole treatment process is by using a group of toxicity tests of different end-points, thus controlling the toxicity or effects of a plethora of pollutants present in water (Barceló et al., 2020).

3. Conclusions

The use of disinfectants has increased amid the ongoing pandemic and is expected to remain elevated (Hora et al., 2020), raising concerns regarding the fate of such chemicals into the environment. In this paper, we collated considerable evidence for the occurrence of hormesis in various organisms exposed to single or combined chemicals used for the production of disinfectants that are widely used during the current pandemic. Such significant sub-threshold responses are of profound importance to be acknowledged, identified, and predicted to avoid potential negative consequences to the environment, ecological processes, and structure and function of communities and ecosystems.

Real-world samples, however, contain a variety of chemicals, not only one specific group of chemicals, and the study of non-linear dose-response relationships induced by complex mixtures is challenging and practically difficult (Docea et al., 2021; Kumari and Kumar, 2020). Inadequate information about the combined exposure to such chemical mixtures also hampers risk assessment under a real-life risk simulation (RLRS) approach (Agathokleous et al., 2019; Hernández et al., 2020). Although this analysis shows hormesis induced by various chemical mixtures, in agreement with the wider literature documenting hormesis induced by diverse chemical mixtures (Agathokleous et al., 2020), new studies are needed to investigate non-linear dose-response relationships induced by diverse mixtures containing disinfectants combined with various other types of chemicals.

Amongst other issues, hormetic effects of disinfectants may stimulate potentially pathogenic bacteria and facilitate the development and spread of drug resistance, implications for risk assessment that can be tackled only if hormetic responses are taken into account. The increasing use of antibiotics around the world (Aslam et al., 2018; Zaman et al., 2017), perplexes the antibiotic removal by the wastewater treatment plants (WWTPs) as well as the antibiotic resistance genes. The aquatic environment already contains traces of antibiotic resistance genes, especially when large hospitals discharge in WWTPs (Kumar et al., 2021; Rodriguez-Mozaz et al., 2015). Hence, assuming that the application of SARS-CoV-2 disinfectants during the COVID-19 pandemic may worsen the situation by adding to the antibiotic resistance issue, advanced WWTP might be needed in addition to changing disinfection formulations.

In conclusion, the present exposition indicates a dilemma of the extensive application of disinfectants against specific human pathogens due to their ability to induce hormesis in various non-target organisms. It also highlights the need for the discovery of alternative products with equal or higher disinfecting ability but with less potential side-effects in order to be prepared when such a massive application of disinfectants is unavoidable.

Credit author statement

Evgenios Agathokleous: Writing- Original draft preparation, Visualization. Damià Barceló: Writing- Reviewing and Editing. Ivo Iavicoli: Writing- Reviewing and Editing. Aristides Tsatsakis: Writing- Reviewing and Editing. Edward J Calabrese: Writing- Reviewing and Editing.

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Author contributions

E.A. drafted the manuscript, had a leading role, served as the hub of communication among the authors, and supervised the production of the manuscript. D.B., I.I., A.T., and E.J.C. reviewed the manuscript and contributed intellectual input. All authors approved the final version for publication.

Declaration of competing interest

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

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