ECOTOX BRASIL
SOCIEDADE BRASILEIRA DE ECOTOXICOLOGIA

Ecotoxicol. Environ. Contam., v. 16, n. 1, 2021, 107-117
doi: 10.5132/eec.2021.01.14

EEC

Environmental concerns about the massive use of disinfectants during COVID-19 pandemic: an overview on aquatic toxicity

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Received September 08, 2019; Accept December 16, 2021

Abstract

Many public health measures to mitigate the spread of SARS-CoV-2 were adopted worldwide, and particularly to the environmental measure of regular cleaning and disinfection of surfaces, the increased use of disinfectant products raises environmental concerns. Quaternary ammonium compounds (QACs), povidone-iodine (PVP-I), chloroxylenol (PCMX) and chlorhexidine (CHX) are the active ingredients of most disinfectant products due to their effectiveness against various microbiological agents. Although presenting antimicrobial efficacy, these biocides have been associated with impacts on aquatic life. For instance, QACs can induce toxicity to *Aliivibrio fischeri* and fish (different species). Gill and liver damages are verified in *Cyprinus carpio* after exposure to PVP-I. CHX induces toxic effects on algae, crustaceans, and fish embryos. PCMX can induce genotoxicity to rainbow trout and malformations on zebrafish embryos, as well as it can reduce the reproduction rate of *Caenorhabditis elegans*. Thus, the potential to cause negative consequences on human and environmental health has resulted in activities from the U.S. and European agencies to favor the use of safer and greener disinfectant products during the COVID-19 pandemic. This review article summarizes the main findings on the impacts of disinfectants (the most used) on aquatic life. This information may help prioritize disinfectants with lower impacts on the aquatic environment for daily use, and especially for high-frequency use as verified in the COVID-19 pandemic. Furthermore, this review may help identify knowledge gaps on the aquatic hazard of disinfectants, which may drive future studies on this matter and, lastly, contribute to the development of sustainable products.

Keywords: SARS-CoV-2; Quaternary Ammonium Compounds; Aquatic Organisms; Greener Alternatives.

INTRODUCTION

The emergence of the new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), family *Coronaviridae*, has become a worldwide concern: it infects humans and can have severe consequences to human health. SARS-CoV-2 was first identified in December 2019 in Wuhan, China; the World Health Organization (WHO)

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declared a world pandemic on March 11, 2020 (de Bruin *et al*., 2020). After SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) in 2002 and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) in 2013, this is the third time a coronavirus has transposed species and infected humans. The disease caused by SARS-CoV-2 is called COVID-19 (Coronavirus Disease 2019) (Perlman, 2020), and has led to a high rate of hospitalization and deaths, producing a significant impact on public health (Pereira, 2020). On September 8, 2021, over 221 million cases of COVID-19 had been reported, and 4.5 million deaths had been registered (WHO, 2021).

Like SARS-CoV and MERS-CoV, SARS-CoV-2 belongs to the β-coronavirus genus. It is an enveloped virus with a diameter of 65–125 nm and single RNA strands. It has four structural proteins: spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) glycoprotein. S glycoprotein, a transmembrane protein, binds to the angiotensin-converting enzyme 2 (ECA2) receptor, thus mediating SARS-CoV-2 entry in the cell. SARS-CoV-2 incubation lasts between 2 and 14 days. Vaccines have been developed and distributed; on September 5, 2021, approximately 5.3 billion vaccine doses were administered (WHO, 2021). However, new SARS-CoV-2 variants are being reported and it will be required some time for an expressive percentage of the population to be vaccinated; in this context, non-pharmaceutical interventions (NPI) are still necessary to avoid the increase in SARS-CoV-2 transmission.

RNA viruses are usually less stable than DNA viruses. However, studies have shown that SARS-CoV-2 is highly stable on different surfaces, which makes surface disinfection an essential measure to control its spread. Van Doremalen *et al*. (2020) compared SARS-CoV and SARS-CoV-2 and found that SARS-CoV-2 in an aerosol formulation is viable for up to 72 hours after the application on different surfaces. Authors also showed that it is more stable on plastic and stainless steel, with a half-life of 6.8 and 5.6 hours, respectively, similar to SARS-CoV (van Doremalen *et al*., 2020). Nevertheless, SARS-CoV has longer viability on a copper surface than SARS-CoV-2 (eight and four hours, respectively). On cardboard, SARS-CoV and SARS-CoV-2 remain viable for 8 and 24 hours, respectively (van Doremalen *et al*., 2020). Another study showed that SARS-CoV-2 is more stable on soft surfaces and can be detected for up to seven days in surgical masks, plastic, and stainless steel and four days in a glass when 5µL of virus culture was pipetted in these surfaces (Chin *et al*., 2020). The results found in both studies may be distinct due to their different methodology.

Furthermore, a study conducted by Vicente and colleagues (2021) detected SARS-CoV-2 RNA in 35 environmental surfaces from a total of 711. Samples were collected from July 2020 to December 2020 and were obtained from primary care units, emergency care units, COVID-19 ward units and intensive care units. Viral RNA was detected on non-disposable instruments (dental reflectors, dental chairs), which were previously disinfected, and on personal items (pens, stamps, notebooks). In primary care units, the frequency of surface contamination was higher than in hospital settings (Vicente *et al*., 2021).

Temperature also affects SARS-CoV-2 viability. A dried culture of the new coronavirus is viable for 3 to 5 days at room temperature (20 ± 5 ºC), 14 days at 4 ºC, and 1 day at 37 ºC. In a solution of minimal essential medium containing 10% fetal bovine serum, SARS-CoV-2 is viable for 7 days at room temperature, 14 days at 4 ºC, and 1 to 2 days at 37 ºC (Chan *et al*., 2020). However, the relevance of these studies for a real-life scenario of exposure to the novel coronavirus has been questioned mainly because the above studies were performed in controlled laboratory conditions with large densities of the virus per sample (Goldman, 2020).

Thus, despite few authors having questioned transmission through fomites, this measure is still among the NPI measures currently adopted by governmental bodies worldwide (*e.g.*, UK, Brazil, EU, USA) to control SARS-CoV-2 transmission in hospitals and non-hospital settings. In addition, disinfection and cleaning surfaces have shown effectiveness in controlling other respiratory viruses, being an NPI measure of relevance for controlling respiratory diseases (Bloomfield *et al*., 2007). Disinfection became standard practice for preventing SARS-CoV-2 in household and hospital settings (Nabi *et al*., 2020).

Disinfection is an efficient tool to prevent the spread of pathogenic microorganisms; however, ingredients of disinfectant products, such as active ingredients, may pose hazard to aquatic organisms. For instance, quaternary ammonium compounds (QACs) present toxicity to algae with EC_{50}96h between 0.1 to 1.8 mg L^{-1}, depending on their alkyl chain length. Also, QACs can induce toxic effects (mortality) on rainbow trout; LC_{50}24h ranges from 0.6 to 41 mg L^{-1}, and these values increase as increase the alkyl chain length of QACs (Hora *et al*., 2020). Therefore, scientifically-based protocols for selecting and proper use of disinfectants are available to minimize the negative impact of these ingredients usage (Centers for Disease Control and Prevention, 2013). Usually, QACs, alcohol, aldehyde, hypochlorous acid, sodium hypochlorite, povidone-iodine (PVP-I), chlorhexidine (CHX) and chloroxylenol (PCMX) are the ingredients responsible for virucidal activity (Pradhan *et al*., 2020).

The United States Environmental Protection Agency (US EPA) offered the Emerging Viral Pathogen guidance to approve disinfectants for use against SARS-CoV-2. The most common active ingredients among the approved disinfectants are QACs (US EPA, 2020a, 2020b), which are widely employed in commercial disinfectant formulations aimed at cleaning and disinfecting hospitals, clinics, and household settings. QACs can inactivate SARS-CoV-2 within 15–30 s of contact in the presence of mucin or bovine serum albumin (BSA) soil load. Thus, the COVID-19 pandemic has caused exposure to QAC-based disinfectants to increase in the last year (Ogilvie *et al*., 2020; Schrank *et al*., 2020).

When it comes to avoiding the transmission of pathogens, disinfectants provide good results, but they often leave

the surface rapidly via evaporation and hand contact. In a pandemic scenario due to a respiratory virus with a high transmissibility rate, different surfaces need to be disinfected more frequently. However, this is not always feasible, mainly in the case of the surfaces of public spaces, such as public transport. In this situation, a long-lasting disinfectant would control transmission more efficiently (US EPA, 2020c). Considering that, US EPA is working on a QAC-based disinfectant that should be effective against SARS-CoV-2 and have a long-lasting effect. QACs are being combined in different types of formulations. To date, US EPA has not conducted experiments with the new coronavirus, but the developed products are promising because they can inactivate the enveloped bacteriophage phi6, a surrogate for SARS-Cov-2 (US EPA, 2020c, 2020d).

This review article revised the literature on the impacts of QACs and other most used biocides, such as povidone-iodine (PVP-I), chloroxylenol (PCMX), and chlorhexidine (CHX), on the aquatic environment. The review article summarizes data on aquatic toxicity, bioaccumulation and biodegradability of the disinfectants. In addition, the article presents sessions addressing changes in cleaning and disinfection habits from consumers and activities from U.S. and European agencies to promote the use of safer and greener disinfectants during the COVID-19 pandemic.

Literature sources used for this review

For the literature search, relevant studies were identified through searching the databases Science Direct, PubMed, and Google Scholar using the keywords 'SARS-CoV-2', 'disinfectants', 'quaternary ammonium compounds', 'chlorhexidine', 'povidone-iodine', 'chloroxylenol', 'toxicity', 'aquatic organisms', 'impacts on aquatic environment', 'biodegradability', 'environmental fate', 'wastewater treatment plants' as well as combination thereof. A restriction was made to only select peer-reviewed studies of English language journals, and there was no restriction regarding the date of the publication. Both original and review articles were considered. Information from registration dossiers for a substance available at the European Chemical Agency (ECHA) was also considered for this review article.

Occurrence of biocides in aquatic environments

Biocides are a group of chemicals that are commonly used as preservatives, antiseptics and disinfectants. Several biocides are high production volume chemicals; thus, they can frequently reach the aquatic environment, and some of them can be adsorbed to sludge and sediment (Östman *et al*., 2017). The entrance sources of biocides into aquatic environments are diverse, but the hospital and domestic effluent discharges outstand (Zhang *et al*., 2015).

For instance, a Swedish study showed that QAC was the most abundant biocide found in STPs, and benzalkonium chloride (BAC) was found in sludge at a concentration of 35 ng L^{-1}. CHX was also presented in STPs, being detected in 67% of the samples, specifically at the incoming sewage water (water and particles). The concentration of CHX in these samples was around 1300 ng L^{-1}; however, this concentration was significantly reduced by 28 ng L^{-1} after treatment. Although a reduction in CHX concentration was verified, this was the first occurrence of CHX in treated sewage waters of Sweden. In addition, the Swedish study also demonstrated the presence of CHX in sludge at a concentration of 8900 ng/g (Östman *et al*., 2017). The presence of PCMX in surface water in concentrations higher than 100 ng L^{-1} was already described in the literature; however, it is reported that it is removed to a high extent during wastewater treatment (Kasprzyk-Hordern *et al*., 2009).

Urban runoff can be another source of biocides' occurrence in aquatic environments. BAC, which is a QAC used to clean roofs and eliminate lichens, moss and algae, was detected in water samples after the roof cleaning process at high concentration ($2.7x10^{-13}$ mg L^{-1}). This concentration can decrease when the total rainfall is around 280 mm (Van De Voorde *et al*., 2012; US EPA, 2006). In addition, BAC was found in sediments of the Hudson River, a river located in U.S., at concentrations ranging from 40 to 8900 ng g^{-1}. Of note, these concentration values were higher than the concentrations of other contaminants (*e.g.*, aluminum and organic carbon). This finding can indicate that the adsorption of QAC into sediments may compromise the effectiveness of wastewater treatment (Li & Brownawell, 2010).

Although we have presented environmental monitoring studies reporting the environmental occurrence of biocides of relevance for the COVID-19 pandemic, the available information is limited, and efforts are required to improve our understanding of the concentration of these biocides in aquatic environments. This information, together with hazard data, may help better predict the risk of these chemical substances for aquatic life.

Changes in consumers' cleaning and disinfection habits: concerns about cumulative toxicity

Over the last months, news and market researchers have reported changes in consumers' behavior. A survey conducted by Statista showed that 41% of males and 49% of females expect to spend more on disinfectant products because of the COVID-19 pandemic (Statista, 2020).

Household cleaning practices have a greater increase in U.S. than in the United Kingdom (UK) after the first reported case of COVID-19. For instance, 44% of consumers in the U.S. use disinfectants at home more frequently, while in UK 37% of consumers have increased the use of these products. Moreover, 18% and 9% of US and UK consumers, respectively, have reported stocking up hard surface cleaners in case of shortage. On the other hand, 24% of UK consumers and 16% of US consumers have not reported any hard surface cleaning habits changes (Novozymes and Conjoint.ly, 2020).

A report by Nielsen (The Nielsen Company (US), 2020) showed increased proactive health shopping. In Brazil, in the first week after the first case of COVID-19 was reported, the

use of antiseptics grew by 623%. In Canada, consumption of alcohol-based hand rub and cleaning products increased by 166% and 15%, respectively, and in the Netherlands and Korea, consumption of soaps increased by levels higher than 200% (The Nielsen Company (US), 2020).

Although raising awareness of the importance of cleaning and disinfection helps control SARS-CoV-2 transmission, the consumers' behavior in using these products may cause human health problems and environmental impacts. In the U.S., 42% of consumers do not follow label instructions during the use of disinfectant products. The ideal procedure is to clean the surface before applying the disinfectant product, letting it air-dry. QACs are commonly found in cleaning and disinfecting products. Incorrect use of these products can be a problem because QACs can irritate the respiratory tract, cause contact dermatitis, and initiate other inflammatory processes (Roberts, 2020; Heikaus, 2020).

There is a gap in the knowledge about the proper use and storage of disinfectants and hand sanitizers, especially among younger than older age groups and among Hispanic individuals compared to non-Hispanic individuals. It was reported a median knowledge score of 5.17 from a maximum of 9.0. This result demonstrated that an effective communication strategy is required to engage consumers in safety precautions (Gharpure *et al*., 2020).

Another concern about the increasing consumption of disinfectant products is their prolonged use. Routine evaluation of acute and chronic toxicity may not reveal the real impact of these compounds on the environment in a pandemic scenario. In fact, assessment needs to be adjusted to consider high-frequency exposure and cumulative toxicity. According to the European Union (EU) Regulation No 528/2012, specific ecotoxicological studies need to be performed to ensure that biocides are used safely. Classification for toxicity to aquatic organisms, short-term toxicity testing on fish and aquatic invertebrates, and bioaccumulation is necessary for these agents to be approved for consumption. To be registered with regulatory agencies, the process of disinfectant development considers the time of exposure and chronic toxicity. Still, the tests in the latter category only predict acute effects. Thus, even chronic tests have not been designed to evaluate the different types of exposure during a pandemic scenario (European Parliament and the Council of the European Union, 2012), which calls for the commercial availability of products with low environmental impact and negligible toxicity.

QAC biodegradability and impact on aquatic life

QACs can reach the aquatic environment through the discharge of WWTP into rivers, oceans, lakes, and estuaries or through the release of raw sewage. Anthropogenic activities, stormwater discharges, runoff and effluent discharge, are the leading cause of the presence of biocides in surface waters (Jardak *et al*., 2016). Therefore, the degradability of these compounds is essential to determine their accumulation in the environment.

QACs are usually biodegraded under aerobic conditions, and the biodegradation pathway starts with mono-oxygenations that depend on O_2 and intracellular NADH (Lai *et al*., 2017). Aerobic QAC degradation is mainly attributed to the *Xanthomonas*, *Aeromonas,* and *Pseudomonas* species (Tezel & Pavlostathis, 2015). Garcia *et al*. (2016) analyzed the biodegradability of five types of QAC-based gemini surfactants. The authors used a standard biodegradation test, the CO_2 Headspace Test (OECD-310), to determine biodegradability. They determined the ultimate biodegradation or mineralization of the surfactants by evaluating the final inorganic products such as carbon dioxide and water. The results showed less than 5% biodegradation after incubation for 28 days, with no differences between surfactants containing a hydrophobic or a hydrophilic spacer (Garcia *et al*., 2016).

QACs have biocide potential and can inhibit the microorganisms that degrade them. Nevertheless, in their review, DeLeo and colleagues (2020) reported that alkyl dimethyl benzyl ammonium chloride (ADBAC) and dialkyl dimethyl ammonium chloride (DADAC) are readily degradable. These authors showed that biodegradation varies from 72% to 100% and from 70% to 90% for ADBAC and DADAC, respectively, depending on the test used to evaluate degradation and chain length (DeLeo *et al*., 2020). The half-life for QAC hydrolysis is estimated at one year at 20ºC; a study with ADBAC determined that this compound is hydrolytically stable (ECHA, 2006 a).

Bioaccumulation depends on the physicochemical properties of the substance and biological features of organisms. QACs have a strong sorption affinity for different environmental materials, bacterial cell walls, and phospholipid bilayer membranes. It suggests that this type of substance can bioaccumulate when in contact with aquatic organisms (Timmer & Droge, 2017; Groothuis et al., 2019). The ECHA registration dossier of dodecyl dimethyl ammonium chloride (DODAC) and alkyl dimethyl benzyl ammonium chloride (ADBAC) presented a bioconcentration factor (BCF) of 8,1 x 107 mg L^{-1} and 7,9 x 107 mg L^{-1} in bluegill fish (Lepomis macrochirus), respectively. However, the carbon chain residues were higher in the skin than in the edible tissues of the fish (ECHA, 2012, 2015). Kierkegaard and collaborators (2020) exposed rainbow trout (*Oncorhynchus mykiss*) to ten alkyl amines and two quaternary alkylammonium surfactants during seven days and reported that bioaccumulation could occur through sorption to external surfaces and systemic uptake. QACs had a higher accumulation in gills than in internal tissues; therefore, systemic uptake of alkylammonium surfactants appears to be very low (Kierkegaard *et al*., 2020).

QAC deposition in the aquatic environment is cause for concern, as summarized in Table 1. Five QACs, namely benzyl dimethyl dodecyl ammonium chloride (BAC-12), decyl trimethyl ammonium bromide (C10TAB), didecyl dimethyl ammonium chloride (DDAC), hexadecyl trimethyl ammonium chloride (ATAC-16), and tetradecyl trimethyl ammonium bromide (C14TAB), are hazardous to aquatic organisms.

Table 1. Toxicity to aquatic organisms after QACs exposure. IC_{50} = Median Inhibition Concentration. Concentration to immobilize 50% of the population for *Daphnia magna* or concentration leading to 50% decrease in bioluminescence for *Aliivibrio fischeri.*

Quaternary ammonium compound	Concentration used in exposure test	IC_{50}	Other toxic effects caused on aquatic organisms	Log Kow	References
Benzyl dimethyl dodecyl ammonium chloride (BAC-12)	0.004-25.0 mg L^{-1} 0.2-2.0 mg L^{-1}	0.17 ± 0.03 mg L^{-1} *Aliivibrio fischeri* 0.6 to 1.1 mg L^{-1} *D. magna*	-	2.93	(Di Nica *et al*., 2017) (Garcia *et al*., 2016) (ECHA, 2006)
Decyl trimethyl ammonium bromide (C10TAB)	0.004-25.0 mg L^{-1} 0.2-2.0 mg L^{-1}	< 1mg L^{-1} *Aliivibrio fischeri*	-	-	(Di Nica *et al*., 2017) (Garcia *et al*., 2016)
Didecyl dimethyl ammonium chloride (DDAC)	0.004-25.0 mg L^{-1} 0.2-2.0 mg L^{-1} 0.4-2.0 mg L^{-1}	0.40 ± 0.06 mg L^{-1} *Aliivibrio fischeri*	Increased mortality of larval walleye, lake sturgeon, and northern pike	≤ 3.0	(Di Nica *et al*., 2017) (Garcia *et al*.., 2016) (Gray *et al*., 2005) (ECHA, 2012)
Hexadecyl trimethyl ammonium chloride (ATAC-16)	0.004-25.0 mg L^{-1} 0.2-2.0 mg L^{-1}	< 1 mg L^{-1} *Aliivibrio fischeri*	-	-	(Di Nica v, 2017) (Garcia *et al*., 2016)
Tetradecyl trimethyl ammonium bromide (C14TAB)	0.004-25.0 mg L^{-1} 0.2-2.0 mg L^{-1}	< 1 mg L^{-1} *Aliivibrio fischeri*	-	-	(Di Nica *et al*., 2017) (Garcia *et al*., 2016)
Benzalkonium chloride (BAC)	0.10-0.105 mg L^{-1} 0.18-0.324 mg L^{-1} 0.4 mg L^{-1} 0.1-5.0 mg L^{-1} 0.03 mg L^{-1}	-	Increased the acetilcholinesterase activity, decreased the catalase activity, increased the levels of thiobarbituric acid-reactive substances, increased the GDI and the erythrocytic nuclear abnormalities in rainbow trout. Caused DNA damage in *D. magna* and *C. dubia* Reduced reproduction, germline toxicity and increased the mortality in *C. elegans.* Induced abnormal dorsal axons in fish embryos. Decrease in chlorophyll a concentrations in *I. galbana* and *C. gracilis* culture. *I. galbana* culture had a negative effect in variable fluorescence. Culture of *C. gracilis* showed a lower variable fluorescence.	2.88	(Antunes *et al*., 2016) (Lavorgna *et al.,* 2016) (Pérez *et al.*, 2009) (Sreevidya *et al.*, 2018) (ECHA, 2006)

In acute exposure, almost all these QACs display IC_{50} (concentration leading to 50% decrease in bioluminescence) values below 1 mg L^{-1} against *Aliivibrio fischeri*. The most toxic are BAC-12 and DDAC, with IC_{50} of 0.17 ± 0.03 mg L^{-1} and 0.40 ± 0.06 mg L^{-1}, respectively (Di Nica *et al*., 2017). A 48-hour immobilization test involving exposure of *D. magna* to QAC gemini surfactants afforded IC_{50} (concentration to immobilize 50% of the population in 48h) ranging from 0.6 to 1.1 mg L^{-1}. In other words, these surfactants are very toxic to aquatic life (acute toxicity I) and toxic to aquatic life (acute toxicity II), respectively (Garcia *et al*., 2016).

DDAC acute toxicity has also been analyzed in three-day-old lake sturgeon (*Acipenser fulvescens*), walleye (*Sander vitreus*), and northern pike (*Esox Lucius*) larvae. At 0.4 to 0.8 mg L^{-1} DDAC, larval walleye and lake sturgeon mortality ranged from 0% to 100%. At 0.8 to 2.0 mg L^{-1} DDAC, larval northern pike mortality varied from 0% to 100%. The LC_{50}96h was 0.45, 0.59, and 1.04 mg L^{-1} for lake sturgeon, walleye, and northern pike, respectively. The concentration of 0.449 L^{-1} of DDAC was reported at stormwater discharge points, and the concentration decreased downstream the discharge site; DDAC is a biocide with high volume production and may

be toxic to aquatic life (Gray *et al*., 2005; Hora *et al*., 2020). Although the presented data about QAC effects on bacteria, microcrustaceans and fish may indicate significant toxicity to aquatic organisms, data about acute, chronic, and cumulative toxicity lack in published studies.

BAC is a known QAC, and it is widely used both as a preservative and biocide in different formulations such as disinfectants and sanitizers (Choi *et al*., 2018). Antunes *et al*. (2016) verified alterations in rainbow trout (*O. mykiss*) chronically exposed to BAC concentrations (0.100–1.050 mg L^{-1}). BAC concentrations as low as 0.180 mg L^{-1} increased acetylcholinesterase activity in the eyes of rainbow trout and decreased catalase activity in the liver and gills. At intermediate BAC concentrations (0.180 and 0.324 mg L^{-1}), the concentration of thiobarbituric acid reactive substances in the gill tissue increased. After the authors performed the comet assay on gill cells, they calculated a genetic damage index (GDI), which increased with rising BAC concentrations. Additionally, compared to the control group, erythrocytic nuclear abnormalities increased in fish exposed to BAC (Antunes *et al*., 2016).

Lavorgna *et al*. (2016) carried out acute exposure experiments on *Daphnia magna* and *Ceriodaphnia dubia* as models and found that BAC damaged DNA in both organisms and that the lowest levels of adverse effect emerged at 4 x 10^{-7} mg L^{-1} BAC for *D. magna* and at 4 x 10^{-6} mg L^{-1} BAC for *C. dubia*. These concentrations are significantly lower, and raise concern about the aquatic impact of BAC (Lavorgna *et al*., 2016).

The toxicity of BAC to phytoplankton has already been described. Chlorophyll concentration in monoalgal cultures of *Isochrysis galbana* and *Chaetoceros gracilis* exposed to BAC decreased. Fluorescence measurements showed that *I. galbana* cultures exposed to 0,03 mg L^{-1} BAC for 1, 24, 48, 72, or 96 h had less intense fluorescence, whereas the fluorescence of *C. gracilis* cultures was less affected by exposure to the same BAC concentration for 1 to 24 h (Pérez *et al*., 2009). Although these data could not explain the mechanisms through which BAC exerts genotoxicity, the use of this biocide and its release in the environment may impact aquatic life.

Chlorhexidine (CHX)

CHX effectively inactivates SARS-CoV-2 on surfaces and objects by interacting with cardiolipin in the virus membrane, thereby disintegrating the phospholipid bilayer of the virus and causing the cell to collapse (Cheung et al., 2012). CHX presents a no observed effect concentration (NOEC) for freshwater sediment of 2.44 mg kg^{-1}, and no significant hydrolysis was reported after tests conducted during 5 days at 50ºC in different pH values. The biodegradability of CHX was tested according to OECD TG 301D, and biodegradation was not observed under the test conditions. The bioconcentration factor of CHX is estimated at 42 kg L-1, and biomagnification via aquatic organisms is not expected (ECHA, 2021).

Aquatic organisms have a different sensibility to toxicants. Therefore, to reduce flaws in ecotoxicity studies, organisms that represent multiple trophic levels must be considered when aquatic toxicity is assessed (Oliveira *et al*., 2018). Jesus and colleagues (2013) studied how CHX affected four organisms in an acute exposure study, the bacterium *Aliivibrio fischeri*, the crustacean *Daphnia magna*, the algae *Pseudokirchneriella subcapitata*, and the fish *Danio rerio* (embryos). On the basis of data regarding the effective concentration to eliminate 50% of the population (EC_{50}), CHX was more toxic to the algae and crustacean (EC_{50}72h was 0.062 mg L^{-1} and EC_{50}48h was 0.045 mg L^{-1}, respectively) (Jesus *et al*., 2013).

For *P. subcapitata*, CHX induced growth inhibition in a dose-dependent manner in 72 hours of exposure. As for the fish embryos and the bacterium, EC_{50}96h was 0.804 mg L^{-1}, and EC_{50}15min was 1.694 mg L^{-1}, respectively. Sublethal effects were also analyzed, and feeding inhibition for *D. magna* was found at EC_{50}6h of 0.5037 mg L^{-1}. CHX presented dose-response toxicity to fish embryos, altered the amniotic fluid with no teratogenic alterations, and caused early hatching at concentrations between 0.04 to 0.64 mg L^{-1}. Analysis of enzymatic biomarkers in the *Danio rerio* embryos showed that cholinesterase induction increased after exposure to CHX at concentrations ranging from 0.08 to 0.9 mg L^{-1}. CHX concentration at 0.9 mg L^{-1} induced catalase, but it did not affect lactate dehydrogenase or glutathione-S-transferase (Jesus *et al*., 2013).

Povidone-iodine (PVP-I)

PVP-I is a biocide commonly used in wound healing, mouth rinse, and aquacultures (Chen *et al*., 2018; Teixeira *et al*.., 2019). It has been demonstrated that PVP-I can inactivate SARS-CoV-2 on different surfaces (Chin *et al*.., 2020). Therefore, this biocide can enter the aquatic environment and is rapidly hydrolyzed, forming different ionic species. PVP-I is not likely to bioaccumulate in the environment, presenting an octanol/water partition coefficient (log Kow) of 2.49 (ATSDR, 2004). Ecotoxicity information about PVP-I is available at the ECHA registration dossier. This document describes that this biocide presents short-term toxicity to fish (*O. mykiss*) and *D. magna* with LC_{50}96h of 1.67 mg L^{-1} and LC_{50}48h of 0.55 mg L^{-1}, respectively. PVP-I is also toxic to algae with EC_{50}72h of 0.13 mg L^{-1}, and in chronic exposure condition, presents NOEC 72h of 0.025 mg L^{-1} (ECHA, 2019).

Hedayati and colleagues (2018) reported that acute PVP-I exposure to common carp (*Cyprinus carpio*) result in histological alterations in gill tissues, indicating damages in gills, such as bleeding, destruction of secondary lamellae, hyperplasia secondary blades, curvature second blade. Bleeding was observed in the lowest concentration (5 mg L^{-1}). Degradation of gill tissue was observed in a dose-response pattern in the concentrations of 5, 7, 8 and 9 mg L^{-1}. In liver tissue, the lesions observed were bleeding, ascite, cell destruction and bile stagnation; these alterations increased in the highest concentration (9 mg L^{-1}); however, the damages caused in the gill were more pronounced (Hedayati *et al*., 2018).

Fish gills are in direct and constant contact with the water; thus, the gill is the first target organ to water pollutants and

is the entry site to toxicants. Therefore, gills are the primary site of toxic effects on the branchial epithelium (Abdel-Moneim *et al*., 2012). The fish gill is a multifunctional organ important to respiration, osmoregulation, acid-base balance and nitrogenous waste excretion, and changes in this structure can lead to an imbalance of these functions. Further, it is commonly recognized that changes in fish gills indicate a response to environmental and chemical stressors (Au, 2004). On the other hand, the liver is an important organ for metabolization and has a key role in the bioaccumulation, biotransformation and excretion of contaminants in fish. Thus, changes in this organ can negatively impact these functions (Triebskorn *et al*., 2002).

Environmental studies describing PVP-I toxicity are still lacking; however, PVP-I is classified in the globally harmonized system of classification and labeling of chemicals (GHS) as toxic to aquatic life with long-lasting effects.

Chloroxylenol (PCMX)

PCMX presents log Kow of 3.27, and it is expected to be adsorbed in suspended solids and sediments. Estimated bioaccumulation of 66 mg L^{-1} was calculated using the log Kow, indicating that CHX has a moderate bioaccumulation capacity. Furthermore, less than 10% of CHX is hydrolyzed after 5 days at 50ºC, presenting a half-life higher than one year (ECHA, 2006 b).

Capkin *et al*. (2017) reported a chronic toxic effect of PCMX on rainbow trout. The comet assay revealed that exposure to 0.0042 ± 0.9 mg L^{-1} PCMX for 40 days had a genotoxic effect on the DNA of red blood cells. Altered gene expression and histopathological lesions such as melanomacrophage center, necrosis, and pyknotic nucleus were also detected in gills, spleen, liver, and kidney trunk of rainbow trout. Abnormal behavior in the exposed animals was not observed in general, except the low feeding rate that was verified. PCMX presents genotoxicity for fish in chronic exposure, according to Comet assay with red blood cells of fish (Capkin *et al*., 2017).

Some studies compared the effects of PCMX and BAC on different aquatic organisms. At concentrations of 0.1 and 1 mg L^{-1} BAC reduced the reproduction of *C. elegans* from 163 ± 7 to 106 ± 9 and 96 ± 5, respectively. PCMX at 1–10 mg L^{-1} also reduced the reproduction of *C. elegans* by 19–39% in a concentration-dependent manner and significantly decreased the lifetime of *C. elegans* from 15 days to 13.2 days. Exposure to PCMX also caused germline toxicity to *C. elegans.* As for the effects of PCMX or BAC on zebrafish embryos, these biocides at 0.5 and 5 mg L^{-1}, respectively, increased the mortality rate. BAC did not cause malformation in the embryos, but PCMX caused pericardial edema and malformation, such as body curvatures in embryos after 72 hours post-fertilization. Moreover, exposure to 0.1 mg L^{-1} BAC induced abnormal dorsal axons in approximately 47% of the analyzed embryos. Embryos with body curvature malformation exposed to PCMX had more abnormal axons projections than embryos without this malformation (Sreevidya *et al*., 2018).

Data regarding non-QAC biocides effects on aquatic organisms are summarized in Table 2. On the basis of the data described in this review, the aquatic effects of biocides increase in the following order (from the least to the most toxic): CHX < PVP-I < PCMX < QACs. Furthermore, it is still a challenge to evaluate the real hazard of chemicals, such as the biocides cited, due to the limitation of amount, quality and type of toxicity information of these and other substances (Dellarco *et al*., 2010).

Greener and safer alternatives

Concerns about the undesirable effects of chemicals on the environment, as well as the increasing demand of consumers for safe and ecological products, have resulted in the active engagement of industry and authorities in the promotion of safer products. Therefore, several safer chemical programs were recently launched in the US and EU, identifying hazardous chemicals and listing chemicals among the safest for functional use (Nonino *et al*., 2021, accepted for publication).

For QAC-based disinfectants, although ecological alternatives can be found, they are still limited. Among the alternatives, accelerated hydrogen peroxide has been reported as an effective antimicrobial and fully degradable in the environment (Omidbakhsh, 2014). Another solution is to use free-rising water cleaners that are equally effective as a disinfectant but are environmentally friendly since chemical residues do not have the potential to accumulate (Rai *et al*., 2020).

It is essential to look for ecolabels on the disinfectant's package. These labels ensure that the product is environmentally friendly. US EPA manages the Safer Choice program, which certifies products that contain safer ingredients. For antimicrobial products like disinfectants and sanitizers, EPA offers the Design for Environment (DfE) label (US EPA, 2020a). However, purchasers that want to acquire safer products need to be aware that there are cautions and limits about certifications—not all are created equal, and "greenwashing" can happen when some certifications declare with little or no transparent information that the products are safer or less toxic to the human health and/or the environment. Credible certifications are usually made by an accredited independent third party. The standards have to be clear and publicly available and must include criteria that require the lab results, assessment of the ingredients to ensure safety individually and in mixtures, and auditing of the production process. Finally, the lack of ecolabels does not mean that the product is toxic to the environment. There are safer products that have not gone through a certification process, or the product can be new and not have received the certification yet (Perlmutter, 2015).

US EPA recommends giving preference to products with minimal presence of harmful chemicals, such as corrosive or irritating substances, substances classified as carcinogens or reproductive toxicants, ozone-depleting compounds,

Table 2. Comparison of non-QAC biocides effects in aquatic organisms. EC_{50} = Median Effective Concentration to eliminate 50% of the population; LC_{50} = lethal concentration in 50% of the population.

Biocide	Concentration used in exposure test	EC_{50} / LC_{50}	Other toxic effects caused on aquatic organisms	Log Kow	References
Cloroxylenol (PCMX)	0.0042 ± 0.9 mg L^{-1} 1.0–10.0 mg L^{-1} 0.5 mg L^{-1}	-	Genotoxic activity, histopathological lesions, melanomacrophage center, necrosis, and pyknotic nucleus in rainbow trout. Reduced the reproduction, germline toxicity and increased the mortality of *C. elegans.* Pericardial edema and body curvatures and abnormal axons projections in zebrafish embryos. DNA damage in *D. magna* and *C. dubia*.	3.27	(Capkin *et al.*, 2017) (Sreevidya *et al.*, 2018). (ECHA registration dossier)
Chlorhexidine (CHX)	0.08-0.9 mg L^{-1}	EC_{50} 6h 503.7 µg L^{-1} Feeding inhibition, *D. magna* EC_{50}72h 62.2 µg L^{-1} Algae EC_{50}48h 45 µg L^{-1} *D. magna* EC_{50}96h of 804 µg L^{-1} Fish embryos	Alterations in the amniotic fluid of fish embryos and early hatching. Increase in cholinesterase and catalase induction in fish embryos.	-	(Jesus *et al.*, 2013)
Povidone-iodine (PVP-I)	5 µg L^{-1} and 9 mg L^{-1} 5, 7, 8 and 9 mg L^{-1}	LC_{50}96h of 1.67 mg L^{-1} Fish (*O. mykiss*) LC_{50}48h of 0.55 mg L^{-1} *D. magna* EC_{50}72h of 130.0 mg L^{-1} Algae	Gill and liver lesions in *Cyprinus carpio.* Degradation of gill tissue.	2.49	(Hedayati *et al.*, 2018) (ECHA registration dossier)

regulated hazardous materials, and chemicals designated as pollutants. Purchase products from renewable resources, including bio-based solvents from citrus, seed, vegetables, and pine oils, is preferable. Also, highly biodegradable and fragrance-free products with low flammability, low toxicity to aquatic species, and pH closer to neutral should be preferred (US EPA, 2020a).

Besides that, regarding disinfection as a protective measure against SARS-CoV-2, Green Seal recommends choosing US EPA List N products with one of the following ingredients: hydrogen peroxide, citric acid, lactic acid, ethyl alcohol (also called ethanol or just alcohol), isopropyl alcohol, peroxyacetic acid, or sodium bisulfate, which are safer options to mitigate SARS-CoV-2 spread (Green Seal, 2020). ECHA also has a list of active substances and products approved for disinfection. The ECHA biocides list considers the environmental impact caused by the disinfection measures. Thus, biocides listed by ECHA seem to be less harmful to the environment and verifying this list before acquiring a product will help select safer disinfectants for the environment. Also, following the labeling instruction of use and disposal is extremely important for the correct use of disinfectants, preventing undesirable effects on the environment (ECHA, 2020).

Although US EPA and ECHA provide information to influence consumers' choices for disinfectant products during the COVID-19 pandemic, there is still a need to develop/discover novel disinfectants from renewable sources with higher biodegradability and lower quality ecotoxicity; thus, safer and greener than the conventional disinfectant products.

CONCLUSION

Cleaning and disinfection of frequently touched surfaces are recommended measures to prevent transmission of SARS-

CoV-2; however, awareness of the impact of the excessive use of biocides is needed. QAC-based disinfectants may be effective against viruses and other microorganisms, but the underlying negative impact in the aquatic environment must be considered. Overall, QACs can present genotoxicity to fish (rainbow trout) and significantly impact the mortality rate of different fish species. CHX increased feed inhibition of *D. magna* and negatively affected fish embryos. PVP-I caused damages on gill and liver of fish (common carp), and PCMX induced malformations in zebrafish embryos and decreased the reproduction of *C. elegans*. Future concerns include overusing biocides that may be genotoxic and mutagenic to aquatic organisms. Therefore, choosing biocides listed by ECHA and US EPA list N with minimal aquatic impact can be a tool to minimize these effects. Giving preference to accelerated hydrogen peroxide, free-rising water cleaners and products of renewable resources over QACs, CHX, PCMX and PVP-I would also be helpful to mitigate aquatic toxicity. In the future, we expect that disinfectants will have long-term effectiveness, higher biodegradability, and minor environmental effects.

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