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A new class of quaternary ammonium compounds as potent and environmental friendly disinfectants

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ABSTRACT
Quaternary ammonium compounds (QACs) are inexpensive and readily available disinfectants, and have been widely used, especially since the COVID-19 outbreak. The toxicity of QACs to humans has raised increasing concerns in recent years. Here, a new type of QACs was synthesized by replacing the alkyl chain with zinc phthalocyanine (ZnPc), which consists of a large aromatic ring and is hydrophobic in nature, similar to the alkyl chain of QACs. Three ZnPc-containing disinfectants were synthesized and fully characterized. These compounds showed 15–16 fold higher antimicrobial effect against Gram-negative bacteria than the well-known QACs with half-maximal inhibitory (IC50) values of 1.43 μM, 2.70 μM, and 1.31 μM, respectively. With the assistance of 680 nm light, compounds 4 and 6 had much higher bactericidal toxicities at nanomolar concentrations. Compound 6 had a bactericidal efficacy of close to 6 logs (99.9999% kill rate) at 1 μM to Gram-positive bacteria, including MRSA, under light illumination. Besides, these compounds were safe for mammalian cells. In a mouse model, compound 6 was effective in healing wound infection. Importantly, compound 6 was easily degraded at working concentrations under sunlight illumination, and is environmentally friendly. Thus, compound 6 is a novel and promising disinfectant.

1. Introduction
Quaternary ammonium compounds (QACs) are a class of disinfectants containing one quaternary nitrogen associated with at least one major hydrophobic substituent (Gilbert and Moore, 2005). In 1915, Jacobs and Heidelberger pointed out that this type of compound had certain bactericidal effects (Jacobs and Heidelberger, 1915). After more than 100 years of development, QACs have now been household disinfectants. For example, 1-cetylpyridinium chloride (CPC) is a commonly used bactericidal active ingredient in mouthwashes, nasal sprays, and throat lozenges (Francesquett et al., 2019; Rezaie et al., 2020). They are also added to dryer sheets and fabric softeners, where their positive charge helps prevent static buildup in the laundry (Hassan, 2014). In addition, QACs are widely used in textiles (Li, Z.S. et al., 2020; Zhang et al., 2018), hospitals (Ogilvie et al., 2021; Schrank et al., 2020), aquaculture (Kaskova et al., 2006), paper industry (He et al., 2015; Zhao et al., 2020), and other fields and for sewage treatment (Liu et al., 2020; Wu and Li, 2008). During the COVID-19 pandemic, the use of QAC disinfectants increased rapidly and exposure to QACs is common, especially in the indoor environment (Zheng et al., 2020).

QACs are mild disinfectants in inactivating viruses and bacteria. Thus, a large amount of QACs is typically needed to remove microbial contamination, posing a threat to the environment. Increased use of disinfectants may accelerate the spread of antimicrobial resistance (Dhama et al., 2021; Hora et al., 2020; Lu and Guo, 2021). In recent years, the health safety of QACs has been a major topic of debate. As early as 2008, Hunt’s group accidentally discovered the mice exposed to QACs (ADBAC, n-alkyl dimethyl benzyl ammonium chloride, and DDAC, dodecyl dimethyl ammonium chloride) in the meals showed reduced fertility (Hunt, 2008), which was further confirmed by Hrubec group in 2014 (Melin et al., 2014). Later, the Hrubec team also found that the QACs caused neural tube defects in rodents (Hrubec et al., 2017).
2.1. Antimicrobial evaluation of PACs to bioluminescent Escherichia coli

Bioluminescent E. coli was grown in LB culture medium at 37 °C under aerobic conditions overnight (6–8 h) to grow until their optical density at 600 nm (OD600) reached about 0.6 (10^8 CFU/mL). The luminance intensity was proportional to the number of live bacteria within a certain range.

The compounds were diluted in DMSO to 10 mM, which was diluted 50-fold with PBS. 2% of CEL (2-chloro-1-(choloromethyl)ethylcarbamate) was included to reduce the aggregation of compounds in an aqueous solution. A concentration gradient was generated starting at 33.3 μM of compounds with 3-fold dilution using PBS containing 2% DMSO and 2% CEL. The concentration gradient of the compounds (100 μL) was then transferred to the opaque 96-well plate containing bacteria. Upon incubation for 30 min in 96-well microplates, the viable fraction S was calculated according to the following formula: $S = (N_1/N_0) \times 100\%$. Here, $N_0$ and $N_1$ were the numbers of colonies in the experimental and control groups, respectively.

2.2. Antimicrobial assays of compound 6 using ATCC standard strains

2.3. MIC determination

2.4. In vivo Antimicrobial test in mammal infection model

To evaluate the anti-bacterial activity of compound 6 in vivo, a local infection mouse model was established according to our previous experimental methods. Adult male Kunming mice (4 weeks old, 25 ± 2 g, purchased from Fuzhou Wu’s Experimental Animal Trade Co. Ltd., Fujian, China) were maintained and handled according to the recommendations of the Institutional Animal Care and Use Committee (IACUC). There were three groups: two were treated with compound 6 and E. coli (ATCC 8739), with or without light, and the other was treated with E. coli only. There were six mice in each group.

Throughout the experiment, mice in all groups were allowed free access to water and food. In this model, the mouse was anesthetized with isoflurane, and the wound (10 mm × 10 mm) was formed by cutting on the back of the mouse with sterile scissors to a depth of 2.0 mm. There was no visible bleeding from the wound. Then each wound of the mouse was inoculated with mid-log phase E. coli (10^5 CFU/mL) (50 μL). One hour later, 50 μL of compound 6 saline solution was added to the wound of the experimental group with a final concentration of 5 μM, and the control group was treated with 50 μL of normal saline. The wound area and body weight of the mice were measured daily. The wounds were washed with 100 μL of 0.9% NaCl on day 2 and incubated on LB agar
plates to assess resistance to infection. Colony formation was observed on LB agar plates. The rate of wound healing was determined by the following equation: \( \text{Wound Recovery} = \frac{S_0 - S_d}{S_0} \times 100\% \). Where \( S_0 \) = wound area at day 0, \( S_d \) = wound area at the specified time of surgery, respectively.

### 2.5. Statistical analysis

Each test was repeated at least three times in the present work. The data were presented as the means ± standard deviations. Statistical analysis was performed using one-way analysis of variance. Additional experimental procedures, including biosafety and antibacterial mechanism of PACs can be found in supplementary materials.

### 3. Results

#### 3.1. Design, synthesis, and characterization of a series of Pc-substituted ammonium compounds (PACs)

The toxicity of conventional QACs raises increasing concern, especially with its greatly increased use since the outbreak of COVID19. Here, the hydrophobic long alkyl chain in the QACs was replaced with zinc phthalocyanine to evaluate their antimicrobial efficacy. Three compounds 4, 5, and 6 were synthesized accordingly to Fig. 1. All compounds (including intermediate compounds) were purified on a C18 reversed-phase column by high performance liquid chromatography (HPLC) to high purity (>98%, Fig. S1 and Fig. S2) and were characterized by ESI-MS (Figs. S3–8). Compound 6, which displayed the best anti-bacterial effects, was fully confirmed by proton NMR (Fig. S9). The UV–Vis spectra of compounds 4, 5, and 6 in DMSO all showed strong absorption at 680 nm, which is characteristic of zinc phthalocyanine (Fig. S10). In DMSO, compounds 4, 5, and 6 all show intense fluorescence emission at 690 nm (ex = 610 nm, Fig. S11).

#### 3.2. Antimicrobial efficacy of the PACs

A bioluminescent \( \text{E. coli} \) strain was used to evaluate the antimicrobial efficacy of the PAC compounds synthesized. The compounds were dissolved in a detergent-containing buffer to ensure all the compounds were in monomeric conformation. Next, the compounds were serially diluted by three-fold dilutions, and mixed with bioluminescent \( \text{E. coli} \), followed by incubation in the dark. The survived \( \text{E. coli} \) was quantified by their bioluminescence intensity. Such antimicrobial assay allowed quick and repeatable measurements of the half-maximal inhibitory curve (IC\(_{50}\)), avoiding systemic errors from, e.g., the fast growth of \( \text{E. coli} \) (20 min doubling time). These cationic compounds showed high anti-bacterial activity against \( \text{E. coli} \) with the IC\(_{50}\) values of compounds 4, 5, and 6 of 1.43 μM, 2.70 μM, and 1.31 μM, respectively (Fig. 2). For comparison, the anti-bacterial activity of two commonly used QAC disinfectants (BC and BB) was also measured using the same assay conditions (Fig. S12). The IC\(_{50}\) of BC and BB against bioluminescent \( \text{E. coli} \) was 19.72 μM and 21.03 μM, respectively. The results showed that our compounds had better anti-bacterial effects than the known QACs. The IC\(_{50}\) of compound 6 was 15–16 times lower than that of BC and BB.

#### 3.3. Antimicrobial effect of the PACs in the presence of light illumination

The ZnPc is a photosensitizer and generates reactive oxygen species (typically singlet oxygen) under the illumination of 680 nm and in the presence of oxygen, which can eliminate nearby bacteria. In our experiments, we found the anti-bacterial effect of the three compounds was further increased in the presence of 680 nm light illumination, giving the IC\(_{50}\) values of compounds 4, 5, and 6 of 0.23 μM, 1.59 μM, and 0.20 μM, respectively (Fig. 3a–c) at a light dose of 15 J/cm\(^2\). A bacterial colony counting method was carried out (Fig. 3d–f) to further validate the antimicrobial efficacy of compound 6. The results showed that compound 6 killed more than 4 logs of \( \text{E. coli} \) and was more effective toward Gram-positive \( \text{S. aureus} \) strain by killing close to 6 logs (>99.9999%) at five times IC\(_{50}\) concentration (1 μM). Importantly, compound 6 showed a significant antimicrobial effect against methicillin-resistant \( \text{Staphylococcus aureus} \) (MRSA) by killing close to 6 logs of bacteria (>99.9999%) at the 5-fold IC\(_{50}\) concentration (Fig. 3g).

#### 3.4. MIC of the PACs against \( \text{E. coli} \), \( \text{S. aureus} \), or MRSA

The minimum inhibitory concentrations (MICs) of the three
compounds at dark were also measured, and were all in the range of 40 μM–160 μM against E. coli, S. aureus, and MRSA. With the assistance of 680 nm light (15 J/cm²), MICs of three compounds against these bacteria were further increased to the range of 20 μM–80 μM. As the control, two conventional disinfectants BC and BB were found to have higher MICs (>640 μM, 40–80 μM, and >640 μM for E. coli, S. aureus, and MRSA, respectively, under identical condition (Table 1).

### 3.5. Biosafety of the PACs

Hemolysis assay was carried out to measure the hemolytic toxicity of the compounds. The results showed, in general, all three compounds had no obvious hemolytic effect (less than 3.6%) at a concentration of 10 μM. Among the three compounds, compound 6 had the lowest hemolysis rate, followed by compound 5, and compound 4 (Fig. 4a). BC and BB showed slightly higher hemolysis at concentrations of 10 μM (about 7%). The cytotoxicity of the compounds toward mammalian cells PC12 (a neuronal cell line) was also measured by the CCK-8 (Cell Counting Kit-8) assay. It was clear that BC and BB were more toxic than compounds 4,
5 and 6 (Fig. 4b and c). The cell survival rates of all three compounds (10 μM) were above 90%, while the cell survival rates of BC and BB at the same concentrations were only about 40%. This data indicates that the three compounds had low toxicity to normal mammalian cells.

3.6. Antimicrobial mechanisms of the PACs

The uptake of the compounds in bacteria was measured by incubating the compounds with *E. coli* for 30 min, washing out the unbound compound, and quantifying the amount of bound based on fluorescence. The results (Fig. 5a) showed that the uptake of the compounds on bacteria increased with increasing concentrations of cationic compounds. Among the three compounds, compound 4 had the highest uptake amount (1.55 nM mg⁻¹ protein). It has been known that the amount of uptake of disinfectants is not always proportional to their antimicrobial efficacy (Zhang et al., 2017).

Next, the reactive oxygen species generation of these three compounds was studied in the presence of bacteria using a fluorescent probe (DCFH-DA). This probe itself has no fluorescence, but becomes fluorescent in the presence of ROS. As shown in Fig. 5b, the fluorescence values of DCF became strong within a short time under light illumination, indicating that all three compounds can produce ROS. Moreover, compound 6 had the highest ROS production among the three compounds. As a control, the bacterial solution alone did not produce ROS.

The type of ROS produced by compound 6 was further studied by electron paramagnetic resonance (EPR) spectroscopy (Fig. 5c and d). No EPR signals were observed in the absence of light illumination. With LED light illumination (15 J/cm²), compound 6 produced strong triplet peaks, a signature of singlet oxygen species. For the hydroxyl radical trap, there was no EPR signal observed, showing no hydroxyl radical generated. These results were consistent with the typical property of phthalocyanine as photosensitizer, where it operates at type 2 mechanism (singlet oxygen), but not type 1 mechanism (hydroxyl radicals).

The effect of compound 6 on the surface morphology of *E. coli* under LED illumination or at dark was investigated by scanning electron microscopy (SEM). The results showed that LED illumination did not affect the morphology of *E. coli*, which was rod-shaped with a smooth surface (Figs. S13a–b). Compound 6 (5 μM) at dark damaged the morphology of the bacteria, causing the bacterial content to flow out (Fig. S13c). Under light illumination, compound 6 became more effective, and the bacterial envelope was completely ruptured (Fig. S13d).

To further study the antimicrobial mechanism of PACs, the integrity of the membrane of *E. coli* (ATCC 8739) were evaluated before or after treatments with the PACs using a fluorescent probe (8-anilino-1-naphthalene-sulfonic acid, ANS), which gives increased fluorescence when binding to the hydrophobic regions of the intact bacterial membrane. Compound 6 showed the strongest fluorescence signal when incubated with *E. coli*, which was further increased after 10 min of LED light irradiation (15 J/cm², 680 nm, Fig. S14).
3.7. Anti-bacterial activity of compound 6 in vivo

Due to its lowest cytotoxicity, compound 6 was chosen for further experiments to evaluate the in vivo antimicrobial efficacy using a mouse model of local bacterial infection (Fig. 6a). The wound healing rates were significantly faster in the treatment groups compared with the control group using saline (Fig. 6b). Infection and ulcers appeared in the control group on the 3rd day after the incision and infection, but not in the treatment groups. The wounds in the treatment groups appeared to harden and became crusty. The bacteria on the wound sites were collected and countered by colony counting experiments the day after surgery (Fig. 6c). The results confirmed the bactericidal effect of compound 6. Wound healing was more evident with the aid of 680 nm light (Fig. 6d). In addition, the bodyweight of mice gained continuously during the experimental period (Fig. 6e), indicating the low toxicity of compound 6 in the mice.

3.8. Stability and environmental safety

The PAC synthesized in this study contains phthalocyanine macrocyclic structures. Phthalocyanine has an absorption in the visible wavelength (~350 nm and 680 nm). Under one Sun irradiation at sea level generated by a sunlight simulator, compound 6 was found to degrade quickly with almost complete degradation in 80 min and 60 min of light exposure at concentrations of 5 μM and 1 μM, respectively. At higher concentrations (1.2 mM or 500 μM), compound 6 degraded much slower (degraded by only 23% or 33% in 120 min of light exposure, Fig. 7a), showing better photostability. The degradation can be fitted with a first-order reaction, giving degradation rate constants of 1.90 × 10⁻³ min⁻¹, 3.00 × 10⁻³ min⁻¹, 2.6 × 10⁻² min⁻¹, and 7.5 × 10⁻² min⁻¹ (Table S1) from high to low concentrations, respectively. The fast degradation of the compound at working concentrations (5 μM and 1 μM) is important for the environment.

Given the fast degradation of the PAC at working concentrations under light irradiation, it is important to evaluate the effect of its degradation products. Here, the compound (200 μL) in a series of working concentrations (1 μM, 2 μM, 5 μM and 10 μM) was illuminated under sunlight (100 mW/cm²) for 4 h until the solution became completely colorless. The cytotoxicity of the compound 6 degraded residuals was evaluated toward a commonly used neuronal cell line (PC12, Fig. 7b). As a control, the light-treated BB and BC (10 μM) still showed highly toxic to PC12 cells, giving only about 40% survival of the cells, and was consistent with the result in Fig. 4c. On the contrary, the degraded compound 6 (10 μM) did not have toxicity to PC12 with a survival rate of over 90%.

Subsequently, the toxicity of the degraded residuals was evaluated on zebrafish. The degradation products of compound 6 were almost nontoxic to zebrafish (3.3% death rate even at a high concentration of 10 μM, Fig. 7c). For comparison, both light-treated BB and BC were significantly more toxic to zebrafish larvae than compound 6 degraded residuals. The lethality of light-treated BB and BC to zebrafish larvae was about 50% at low concentrations (1 μM). It should be pointed out that, without the light-induced degradation, compound 6 at 2 μM concentration was non-toxic to zebrafish, and at the high concentration (5 μM and 10 μM), the mortality of zebrafish was only 6.7% and 13.3%, respectively (Fig. S15). The intact BB and BC led to about 80% of zebrafish death at 5 μM, and nearly all zebrafish died at 10 μM.

Next, whether compound 6 degraded residuals could still kill microorganisms was evaluated. It turned out that the sunlight-exposed compound 6 killed only 0.7% of bacteria (Fig. 7d), while the light-exposed BB and BC killed almost all the bacteria (>99.9%). The results indicated that compound 6 degraded residuals did not have an antibacterial effect on environmental microorganisms, which is beneficial for ecological protection.

It should be emphasized that compound 6 has excellent photo stability under light-protected conditions. Compound 6 showed almost no...
degradation at either low (5 μM and 1 μM) or high (1.2 mM or 500 μM) concentrations, or in the solid state, in the absence of light exposure (more than 10 days, see Fig. S16) at room temperature. Such properties favor the storage stability of compound 6.

4. Discussion

Approximately 32.5% of QACs produced worldwide are reported to be released into the environment, and retain their biocidal properties (Kim et al., 2018; Tezel and Pavliostathis, 2011). These QACs are resilient to natural degradation and pose serious environmental hazards (Badmus et al., 2021). The global average concentrations of QACs in domestic wastewater, treated sewage, and surface water was reported to be about 500 μg L$^{-1}$, 50 μg L$^{-1}$ and 40 μg L$^{-1}$, respectively (Li and Brownawell, 2010; Ruan et al., 2014). The ecotoxicologically effective concentrations (EC$\text{50}$) of QACs for various fish, algae, crustaceans, daphnia, rotifers, bacteria, and protozoa ranged from a few tens of μg L$^{-1}$ to mg L$^{-1}$ (Zhang et al., 2015). In addition, it has been shown that QACs have potential genotoxic effects on exposed eukaryotic cells at concentrations commonly found in wastewater (Feek et al., 2007). Biodegradation is the main removal pathway of QACs from the environment (Zhang et al., 2015). Various factors affect the biodegradation of QACs, such as QACs' chemical structure, concentration, and complexing with anionic surfactants and microbial community acclimatization (Brycki et al., 2014; Qin et al., 2005). Besides, QACs are generally considered to be stable to direct photo degradation. The half-life of photolysis in the natural environment is expected to be 12–94 days (Hora and Arnold, 2020). Thus, new cationic disinfectants with enhanced biodegradability are under actively development (Garcia et al., 2019; Thorsteinsson et al., 2003).

Our PAC compounds appear to be quite safe. The phthalocyanine-type compound is generally safe and has been used as a color dye for outfits and underwear in the fabric industry for decades. This type of compound has also been used as an anti-tumor drug (Photosense®) for cancer treatment in Ukraine since the 1990s (Smirnova et al., 2005). Another phthalocyanine-based compound (Photocyanin®) is currently under Phase II clinical trial for esophagus cancer in China (Chen et al., 2020; Li, S. et al., 2020a). Its Phase I trial demonstrated no major adverse effect in humans at a dose of 2 mg/kg. Phthalocyanine green has been approved by FDA (2020) to use in contact lens, surgical sutures, and latex condoms as a color additive. Phthalocyanine was also approved by FDA as Indirect Additives used in food contact substances.

PAC can be degraded when exposed to light illumination. The degradation is concentration-dependent with the PAC at millimolar range degraded much slower than at micromolar concentration. This is a favorable property for the environment and for storage: as the PAC is released into the environment, it will be diluted and degraded easily by natural light. For long-term storage, the compound should be kept off direct light illumination to increase its stability. It should be emphasized that the compound is very stable, either in liquid or in solid state, in the absence of light exposure (more than 10 days, see Fig. S16) or in the solid state at room temperature. We also measured the anti-bacterial effect of compound 6 after 10 days’ storage in liquid form, and found that its anti-bacterial effect remained the same (IC$\text{50}$ of 1.30 vs 1.31 μM at dark).

Compared to QACs, the PACs reported here are more easily degradable, especially their largest fragment, phthalocyanine. Phthalocyanine degradation and the degradation products are well studied in the laboratory. Factors that affect metal phthalocyanine stability include its molecular structure, the type of central metal ion, solvent, and oxygen. In microorganism-induced degradation of copper phthalocyanine by a type of fungus (P. chrysosporium), extensive destruction of the phthalocyanine ring was observed followed by the release of free copper ions. The major metabolite was identified as phthalimide based on comparing capillary electrophoresis migration times and liquid chromatography retention times of standard molecules (Conneely et al., 2002). The oxidative enzyme also induced degradation of Cu(II)-phthalocyanine-based reactive dyes in a soybean peroxidase/H$_2$O$_2$ system, allowing the oxidation of isoinsoles to sulfophthalimide by destroying the macrocyclic structure and releasing copper(II) ions (Marchis et al., 2011). In other reports, UV lights was found to induce rapid degradation of metal phthalocyanines, including ZnPc, yielding phthalimide as the main degradation product (d’Alessandro et al., 2005; Slota and Dyrda, 2003). The presence of phthalimide as the degradation intermediate is interesting and indicates the presence of oxygen nearby the bridging nitrogen atoms. Thus, it is not surprising that the amount of oxygen adsorption affects phthalocyanine photodegradation (Slota and Dyrda, 2003). These studies consistently point out the phthalimide and the metal ion as key degradation intermediates. Phthalimide is not a stable molecule, and will certainly undergo further reaction or fragmentation. There are no detailed studies on the environmental degradation of phthalocyanine. However, these laboratory degradation studies showed PAC-based disinfectants can be degraded into small fragments, and thus are a class of environmentally friendly disinfectants. Further studies are needed to assess their long-term safety and environmental impact.
5. Conclusions

In summary, the QACs were modified by replacing the long lipophilic chains with phthalocyanine macrocyclic structures. This modification enhanced the anti-bacterial effect with compound 4 or compound 6 reaching nanomolar levels of IC50 in the presence of light illumination. Moreover, compound 6 showed a good antimicrobial effect against S. aureus and MRSA. Under sunlight exposure, these compounds degrade rapidly at working concentrations. This study opens up a new avenue to construct clean, safe and environmentally friendly disinfectants.

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Appendix A. Supplementary data

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References

Badmus, S.O., Amusa, H.K., Oyehan, T.A., Saleh, T.A., 2021. Environmental risks and toxicity of surfactants: overview of analysis, assessment, and remediation techniques. Environ. Sci. Pollut. Res. Int. 28 (44), 62085–62104. https://doi.org/10.1007/s11356-021-16483-w.

Bello, A., Quinn, M.M., Perry, M.J., Milton, D.K., 2009. Characterization of occupational exposures to cleaning products used for common cleaning tasks—a pilot study of household cleaners. Environ Health Glob 8 (11). https://doi.org/10.1186/1476-069x-8-11.

Brycki, B., Waligorska, M., Szulc, A., 2014. The biodegradation of monomeric and dimeric alkylationammonium surfactants. J. Hazard Mater. 280, 797–815. https://doi.org/10.1016/j.jhazmat.2014.08.021.

Chen, D., Song, M.R., Huang, J.L., Chen, N.S., Xue, J.P., Huang, M.D., 2020. Photocyanine: a novel and effective phthalocyanine-based photosensitizer for cancer treatment. Journal of Innovative Optical Health Sciences 13, 2030009. https://doi.org/10.1142/S1793545820300094.

Connelly, A., Smyth, W.F., McMullan, G., 2002. Study of the white-rot fungal degradation of selected phthalocyanine dyes by capillary electrophoresis and liquid chromatography. Anal. Chim. Acta 451 (2), 259–270. https://doi.org/10.1016/S0003-2670(01)01415-5.

d’Alessandro, N., Tonucci, L., Morvillo, A., Dragni, L.K., Di Deo, M., Bressan, M., 2005. Thermal stability and photostability of water solutions of sulfophthalocyanines of Ru (II), Co(II), Ni(II), Fe(II) and Co(II). J. Organomet. Chem. 690, 2133–2141. https://doi.org/10.1016/j.jorganome.2005.01.022.

Datta, S., He, G., Tomilov, A., Sahdeo, S., Denison, M.S., Cortopassi, G., 2017. In vitro evaluation of mitochondrial function and estrogen signaling in cell lines exposed to the antiestrogen cetylpyridinium chloride. Environ. Health Perspect. 125 (8), 087015. https://doi.org/10.1289/EHP1404.

Dhama, K., Patel, S.K., Kumar, R., Masand, R., Rana, J., Yatoo, M.I., Tiwari, R., Sharun, K., Mohapatra, R.K., Natesan, S., Dhawan, M., Ahmad, T., Emran, T.B., Malik, Y.S., Harapan, H., 2021. The role of disinfectants and sanitizers during COVID-19 pandemic: advantages and deleterious effects on humans and the environment. Environ. Sci. Pollut. Res. Int. 28 (26), 34211–34228. https://doi.org/10.1007/s11356-021-14429-w.

Dumas, O., Varacco, R., Boggio, G.M., Quinot, C., Zock, J.P., Hennebroek, P.K., Speizer, F.E., Le Mouéil, N., Camargo, C.A., 2019. Association of occupational exposure to disinfectants with incidence of chronic obstructive pulmonary disease among US female nurses. JAMA Netw. Open 2 (10). https://doi.org/10.1001/jamanetworkopen.2019.13563.

Ferk, F., Misiuk, M., Hoelzl, C., Uhl, M., Fuerbacher, M., Grillitsch, B., Parzefall, W., Nersesyan, A., Micetia, K., Grummert, T., Ehrlich, V., Kramsuller, M., 2007. Benzalkonium chloride (BAC) and dimethyldioctadecyl-ammonium bromide (DDAB), two common quaternary ammonium compounds, cause genotoxic effects in mammalian and plant cells at environmentally relevant concentrations. Mutagenesis 22 (6), 363–370. https://doi.org/10.1039/mutage/gem027.

Food and Drug Administration, 2020. Summary of color Additives for use in the United States in foods, drugs, cosmetics, and medical devices. https://www.fda.gov/food/color-additives-summary-color-additives-use-united-states-foods-drugs-cosmetics-medical-devices.

Francesquetti, J.Z., Rizzetti, T.M., Cadaval, T.R.S., Prestes, O.D., Adame, M.B., Zanella, R., 2019. Simultaneous determination of the quaternary ammonium pesticides parquat, diquat, chloromequat, and meipquat in barley and wheat using a modified quick polar pesticides method, diluted standard addition calibration and hydrophilic interaction liquid chromatography coupled to tandem mass spectrometry. J. Chromatogr. A 1592, 101–111. https://doi.org/10.1016/j.chroma.2018.12.060.

Garcia, M.T., Ribosa, I., Guindulain, T., Sanchez-Leal, J., Vives-Rego, J., 2001. Fate and effect of monoaoyl quaternary ammonium surfactants in the aquatic environment. Environ. Pollut. 111 (1), 169–175. https://doi.org/10.1016/S0269-7499(00)00232-X.

Garcia, M.T., Ribosa, I., Kowalczyk, I., Pakiet, M., Brycki, B., 2019. Biodegradability and aquatic toxicity of new cleavable betainate cationic oligomeric surfactants. J. Hazard Mater. 371, 108714. https://doi.org/10.1016/j.jhazmat.2019.03.005.

Gilbert, P., Moore, L.E., 2005. Cationic antiseptics: diversity of action under a common epithet. J. Appl. Microbiol. 99 (4), 703–715. https://doi.org/10.1111/j.1365-2672.2005.02664.x.

Hassel, M.M., 2014. Enhanced antibiotic and mechanical properties of corona plasma treated wool fabrics treated with 2,3-epoxypropyltrimethylammonium chloride. Ind. Eng. Chem. Res. 53 https://doi.org/10.1021/acs.earl.5b00447.

He, M., Xiao, H.H., Zhou, Y.M., Lu, P., 2015. Synthesis, characterization and antimicrobial activities of water-soluble amphiphilic copolymers containing ciprofloxacin and quaternary ammonium salts. J. Mater. Chem. B 3 (18), 3704–3713. https://doi.org/10.1039/c5tb00028g.

Herron, J., Reese, R.C., Tallman, K.A., Narayanaswamy, R., Porter, N.A., Xu, L., 2016. Identification of environmental quaternary ammonium compounds as direct inhibitors of cholesterol biosynthesis. Toxicol. Sci. 151 (2), 261–270. https://doi.org/10.1095/toxsci/ksw041.

Herron, J.M., Hines, K.M., Tomita, H., Seguin, R.P., Cull, J.Y., Xu, L., 2019. Multi-omics investigation reveals benzalkonium chloride disinfectants alter steroid and lipid homeostasis in the mouse neonatal brain. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfz139.

Hora, P.I., Arnold, W.A., 2020. Photocatalytic fate of quaternary ammonium compounds in river water. Environ Sci Proc Imp 22 (6), 1368–1381. https://doi.org/10.1039/d0em00086h.

Hora, P.I., Pati, S.G., McNamara, P.J., Arnold, W.A., 2020. Increased use of quaternary ammonium compounds during the SARS-CoV-2 pandemic and beyond: consideration of environmental implications. Environ. Sci. Technol. Lett. 7 (9), 622–631. https://doi.org/10.1021/acs.estlett.0c00437.

Ibrahimi, M., Melin, V.E., Shear, C.S., Ferguson, E.E., Garofola, C., Repine, C.M., Chapman, T.W., Patel, H.R., Ravzi, R.M., Sgueura, J.E., Potinîen, H., Magnus-Bisell, G., Hunt, P.A., 2017. Ambient and dosed exposure to quaternary ammonium
