Spin-off company dell'Università di Camerino

LITERATURE REVIEW ON dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride

FROM 2010 TO 2020

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1. GENERAL INFORMATION

Chemical nomenclature: dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride

(CAS-No.) 27668-52-6

Chemical category: Si-QAC Quaternary ammonium organosilane coatings. Quaternary ammonium compounds (QAC)s represent a diverse and large group of compounds with 191 compounds listed in the PAN Pesticides Database. (1) Conventionally the term QAC refers to the subgroup of linear alkyl ammonium compounds that are composed of a hydrophobic alkyl chain and a hydrophilic counterpart. For antimicrobial treatments mainly the compounds containing long alkyl chains (12–18 carbon atoms) have been used.

Molecular Structure:

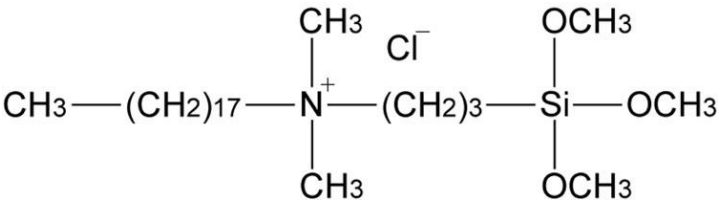

Fig. 1 Molecular structure of **dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride**

2. MECHANISM OF ACTION

Dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride is commonly applied to several types of surfaces, where it covalently links, showing a "non-migrating antimicrobial effect". (2) The silan (trimethoxysilyl) base of the molecule is capable of covalently bonding many types of surface, including glass, ceramics, wood, polymers and metals, with an exceedingly high adhesion strength.

The positively charged middle section of the molecule is effective in promoting the migration of microorganisms onto the chain structured tip section of the molecule. The outer cellular membranes of bacteria and fungi are hydrophobic, as are lipid envelopes of some viruses, and also possess a net negative charge. It was, therefore, reasoned (65–74) that certain surface-attached, long-chained hydrophobic polycations (e.g., QACs) should be able to interact with these membranes, to disrupt the membrane's molecular order, and to kill the host microbe. (3)

The spike field obtained by such a barrier coating on the surface causes the membrane of the microorganism to be punctured with catastrophic collapse avoiding microorganism colonies or floccules to form (Figure 2). The coating can easily be tailored to a homogeneous, uniform molecular monolayer which will function as an antimicrobial barrier with only physical action (Figure 3). (4)

Quaternary ammonium compounds such as Si-QACs irreversibly bind to the phospholipids and proteins of the membrane, thereby impairing membrane permeability. (5)

The mechanisms of action of QAS causing death in yeast is not known, but it seems to impede the formation of hyphae. (6)

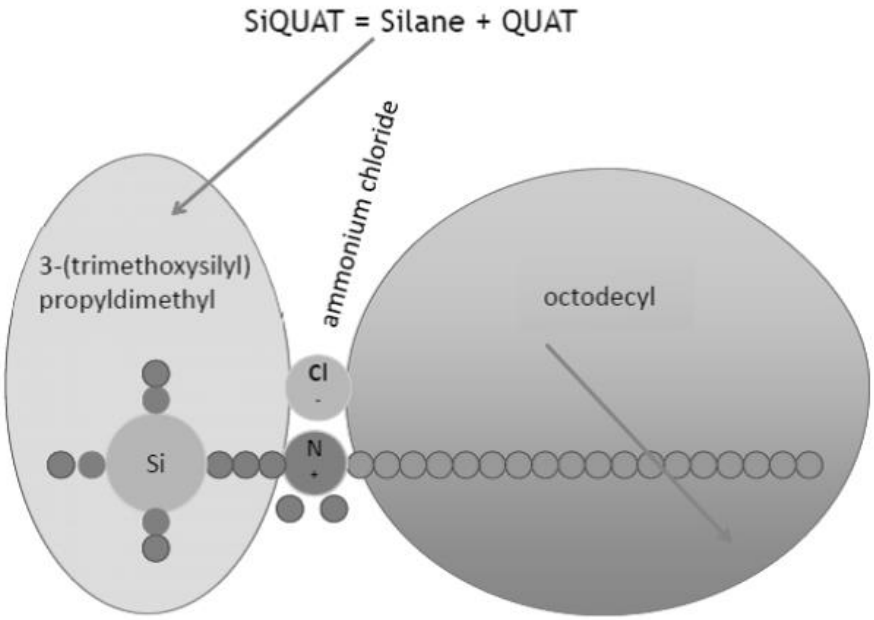

Figure 2. Schematic structure of a representative barrier molecule (7)

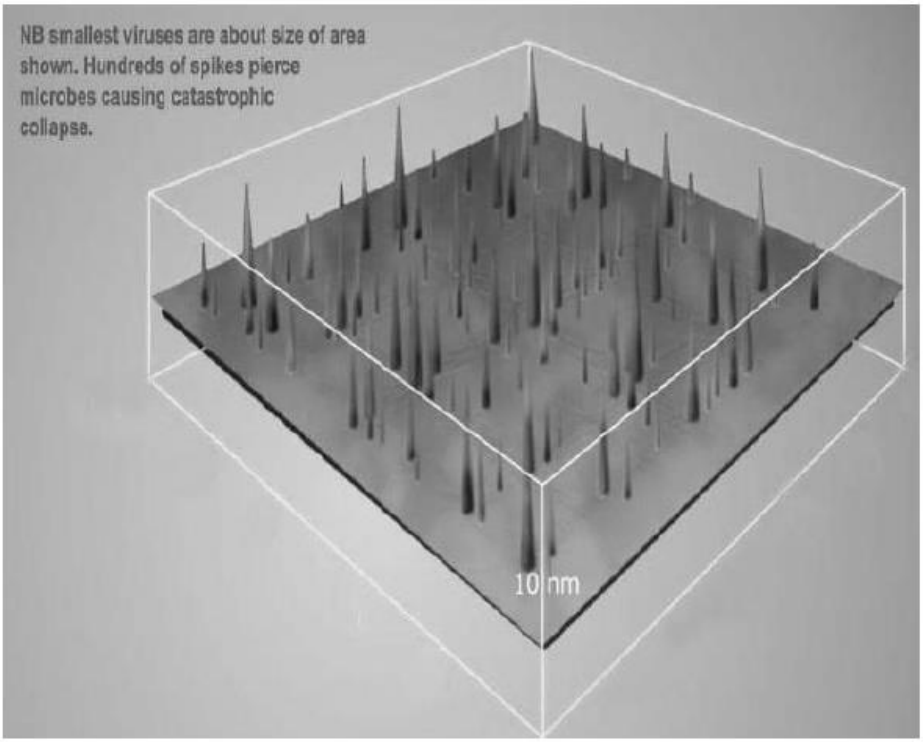

Figure 3. Schematic SEM image of an antimicrobial molecular barrier obtained by coating with a **dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride** solution (7)

The molecular barrier comprises of 3-(trimethoxysilyl)-propyl dimethyl octadecyl ammonium chloride molecules polymerizes with each other through Si-O-Si bonds, and covalently bonded on the substrate surface by Si-O-M bonds (M represents metal, metalloid or carbon atoms on the surface) forming a surface network of molecular spikes (Figure 4).

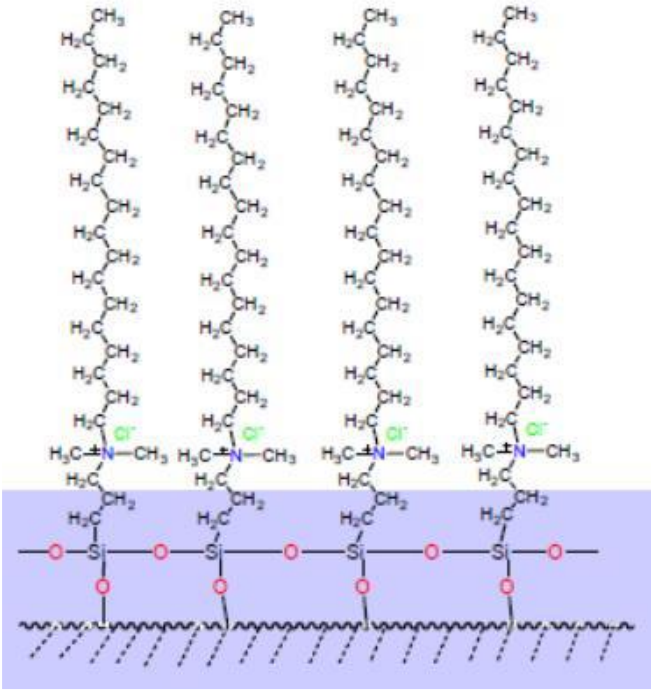

Figure 4. Molecular barrier network molecules covalently bonded on substrate surface (8)

The surface covalent bonding of the 3-(trimethoxysilyl)-propyl dimethyl octadecyl ammonium chloride molecules on the substrate surface, as well as their polymerization by bonding with each other to form a surface network is due to the sequential hydrolysis and condensation reactions of the trimethoxysilyl (-Si-O-CH3-) groups. After the hydrolysis one or more of the probable aquo (-Si-OH2), hydroxo (-SiOH), and/or oxo (Si=O) ligand groups are formed. Condensation occurs through olation (-Si-OH-Si-) and oxolation (-Si-O-Si-) reactions. Condensation via alcoxolation is also probable.(8)

Adavanteges of Dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride over migrating antimicrobials: Silver or copper absorbed in zeolite or TiO2 carriers, biguanide, chitosan, bis-chlorinated phenols (Triclosan), organo-tin compounds (TBT), heavy metal (Pb, Hg, As)-organo complexes, water soluble quaternary compounds distributed in a surface coating or impregnated in a body constitute examples of migrating antimicrobials. The

mechanism of action of migrating antimicrobials is the leaching or diffusion of the active component in a wet or humid environment to be taken up by microorganisms. Their disadvantage is the gradual loss of the effectiveness, and the generation of resistant microorganism strains. The non-migrating antimicrobials are fixed on a surface and cannot be consumed by microorganisms, hence, do not have the disadvantages related to the migration of the active component.

3. COATED SURFACES

TYPE OF SURFACE	SUPPORTING REFERENCES
Coated SiO2 nanoparticles (QAS-SiO2)	(9) (10) (11) (12)
Quaternary ammonium polyvinylidene fluorine membrane	(13)
Coated or loaded microparticles	(14) (15)
Coated TiO2 nanoparticles	(16) (17)
Cellulose membrane	(18) (19) (20)
Polyvinyl alcohol membrane/particle	(19) (21)
Glass	(19) (10)
Coated silica sand	(22)
Coated PNIPAAM/chitosan microgels	(23)
Coated SiO2 nanocapsules	(24)
Poly vinyl chloride panels	(24) (12)
Silicone rubber tracheoesophageal shunt prostheses	(6)
Ceramic	(4)
Polyethylene	(25)

Polystyrene	(25)
Polypropyl methacrylate grafting	(26)
Cotton fabric	(27) (16) (23) (28) (26) (29)
Hydroxyapatite composite microparticles	(30)
Kevlar fabric (synthetic fabric)	(31)
Polysulfone (PSF)/SiO2 hybrid capsules	(14)
Metal-free quaternized carbon dots	(32)
Polyester fiber	(33)
Wood	(34)
Latex	(15)
Microcapsule encasing the product coated with the product	(35)
Facemasks	(35)
Methylcellulose polymers, hydroxypropyl methylcellulose polymers, and combinations thereof	(36)
Polymeric skin scaffold of 1 - Octadecanaminium N, N dimethyl [(3 - trihdroxysilyl) propyl] chloride , silk protein, polyhexanide and mixtures thereof	(37)
Natural or nitrile rubber latex	(38)
h-BN nanoplatelets	(39)

4. COATING METHODS

a) Most of the reported literature applies spray-coating or soaking procedures using a low pH solution pH = 3) to promote chemical bonding.
E.g. Interaction of trimethoxysilane with hydroxyl bearing materials may proceed through the following steps:
(i) Hydrolysis: In the presence of water, alkoxy groups can be hydrolyzed to liberate the corresponding alcohols and generate reactive silanol groups.
(ii) Selfcondensation: Once the silanol groups form in the solution, the concomitant condensation between silanol groups also starts, therefore generating a siloxane (Si O Si) polymer network in the solution. An acidic pH environment is usually preferable to accelerate the hydrolysis rate.
(iii) Adsorption: When hydrolyzed silane solutions are mixed, for example, with cotton fibers, the reactive silanol monomers or oligomers have a high affinity for each other, forming rigid polysiloxane structures linked with a stable Si O Si bond and for the hydroxyl sites of fibers via hydrogen bonds.
(iv) Grafting: Heating may remove the water or solvents in the fibers and drive the dehydration reaction at the adsorption sites between silanols and fiber hydroxyl groups thereby forming the covalent Si O C bonds. Heating also promotes the condensation of free silanol groups resultantly forming the solid polysiloxane layers on the fiber surface. Hydrogen bonding is also possible between the Si O Si backbone and the hydroxyl groups of materials. (28)

b) Air ozonolysis (25)

c) Thermal curing coating process, Pad-dry/pad-dry-cure processes (26) (29) (40) (20)

d) Foam Application (40)

e) Atomization (41)

f) Spray , foam , mist , fog or wipes (42)

h) Atmospheric Pressure Plasma-Induced Graft Polymerization (31)

i) Pickering Emulsion Polymerization (14)

j) Solvothermal treatment (32)

k) "Reverse gravure" and "Meyer bar" (33)

l) Impregnation prior acidification (34)

m) Soaking, impregnating, mixing, painting, spraying, injecting, and via aerosols (43)

n) Spraying, dipping, laundering, soaking, brushing, and/or rolling the substrate with the antimicrobial composition (21)

o) Electrostatic sprayer (positive charge) (17)

5. APPLICATIONS

APPLICATION	SUPPORTING REFERENCES
Hydrophobic coating for underwater surfaces with anti-fouling and antibacterial properties	(9) (14) (24) (12)
Wastewater treatment, treatment of drinking water	(13) (18) (22) (41)
Textile manufacturing, as biocides and as auxiliaries at different stages of the manufacturing process, e.g. during pretreatment, for coloring and finishing, as conditioning, antistatic or softening agents and as detergents	(27) (16) (23) (28) (26) (31) (29) (44) (33) (40) (21)(45)(20)
Surface disinfectants in the food sector	(46) (47) (18) (3) (36) (48)
Plant protection products and pharmaceuticals	(49)
Glass surface coating	(10)
Surface disinfectants in the medical field, including medical devices and surfaces	(18) (6) (50)(51)
Ceramic tiles coating	(4)
Dentistry, dental bite	(30)
Theranostic (simultaneous imaging, eliminating, and inhibiting bacterial biofilms)	(32)

Wood preservation	(34)
Poultry houses, including cages and equipment, farm and transportation vehicles for animals, foot and tire dips, walls, ceilings, floors, and fixtures found in food processing plants, refrigerators and coolers, surfaces found in broiler and breeder farms, hatchers, setters, evaporative coolers, humidifying systems, and ceiling fans found in hatcheries, Surfaces found in Zoos, emergency vehicles, homes, offices and automobiles, hotels, motels, schools, day care centers, hospitals, contagious illness rooms, and correctional facilities	(43)
Paint formulation	(15)
Prevention and treatment of infection in humans and animals	(35)
Sanitizing wet wipes	(17)
Topical antiseptic	(37)
Antiseptic gloves	(38)
Medical electronic devices	(39)

6. BIOCIDAL ACTIVITY

TYPE OF PATHOGEN	**SUPPORTING REFERENCES**
GRAM POSITIVE BACTERIA	
Bacillus sp. (vegetative cell)	(41)
Corynebacterium diptheriae	(41)
Micrococcus lutea	(41) (37)
Micrococcus sp.	(41)
Mycobacterium tuberculosis	(41) (37)
Mycobacterium Smegmatis	(41)

Propionibacterium acnes	(41)
Streptococcus faecalis	(41) (36) (37) (42)
Streptococcus mutans	(41) (36) (37) (42)
Streptococcus pneumonia	(41) (36) (37) (42)
Streptococcus pyogenes	(41) (36) (37) (42)
Bacillus cereus	(19) (37) (42)
Alicyclobacillus acidoterrestris	(19) (37) (42)
Staphylococcus aureus	(13) (14) (16) (10) (4) (6) (28) (26) (12) (30) (31) (32) (44) (40) (43) (41) (36) (17) (37) (42) (39)
Staphylococcus enteritis	(36) (37) (42)
Bacillus anthraces (anthrax)	(43) (37) (42)
Bacillus atrophaeus spores	(43) (42)
Listeria monocytogenes	(51)[1] (36)
Lactobacillus	(36)
Bacillus subtilis	(25)
Rothia dentocariosa	(6)
Staphylococcus epidermidis	(6) (37)
Streptococcus salivarius	(6) (37)
Deinococcus geothermalis	(10)
Brochothrix thermosphacta	(36)
GRAM-NEGATIVE BACTERIA	
Acinetobacter calcoaceticus	(41) (37)
Acinetobacter johnsoni	(36) (37)
Aeromonas hydrophilia	(41) (37)
Citrobacter deversus	(41) (37)
Citrobacter freundi	(41) (37) (42)
Enterobacter aerogenes	(41) (36) (42)
Enterobacter aglomera	(41)(36) (37) (42)
Escherichia coli	(41) (13) (16) (10) (18) (19) (22) (23) (25) (28)(26) (12) (30) (32) (33) (43) (15) (36) (37) (42) (39)
Klebsiella Oxytoca	(41) (37) (42)
Klebsiella pneumoniae	(41) (37) (42)
Klebsiella terriena	(41) (37) (42)
Legionella pneumophila	(41) (37) (42)
Morganella morganii	(41) (37) (42)

Proteus mirabilis	(41) (37) (42)
Proteus vulgaris	(41) (37) (42)
Pseudomonas fluorescens	(41) (36) (37) (42)
Salmonella cholera suis	(41) (37) (42)
Salmonella typhi	(41)(37) (42)
Salmonella typhimurium	(41) (42)
Serratia liquifaciens	(41) (42)
Xanthomonas campestris	(41) (42)
Pseudomonas aeruginosa	(19) (4) (43) (41) (37) (42)
Shewanella loihica	(9) (37)
Salmonella sp.	(51)[1] (37)
Clostridium difficile spore	(50)
Clostridium perfringen	(36) (37)
Clostridium botulinum	(36) (37)
Shigella	(43) (36) (37)
Salmonella enterica	(25) (36) (37)
Pseudomonas fragi	(36) (37) (42)
Pseudomonas lundensis	(36) (37) (42)
Campylobacter jejuni	(36) (37) (42)
Vibrios cholera (including serotypes O1 and non - 01	(36) (37) (42)
Vibrio parahaemolyticus	(36) (37)
Vibrio vulnificus	(36) (37)
Yersinia enterocolitica	(36) (37)
Yersinia pseudotuberculosis	(36) (37)
Moraxella	(36) (37)
Psychrobacter immobilis	(36) (37)
Shewanella putrefaciens	(36) (37)
Serratia	(36) (37)
VIRUSES	
Adenovirus Type II	(41) (18) (22) (37) (42)
Adenovirus Type IV	(41) (37) (42)
Bovine Adenovirus Type I	(41) (37) (42)
Bovine Adenovirus Type IV	(41) (37) (42)
Feline pneumonitis	(41) (37) (42)
Herpes Simplex Type I	(41) (37) (42)

[1] In combination with other biocides

Herpes Simplex Type II	(41) (37) (42)
HIV-1(AIDS)	(41) (37) (42)
Influenza A2 (Asian)	(41) (37) (42)
Influenza B	(41) (37) (42)
Mumps	(41) (37) (42)
Parinfluenza (Sendai)	(41) (37) (42)
Reovirus Type I	(41) (37) (42)
Influenza A2 (Aichi)	(41) (37) (42)
Simian Virus 40	(41) (37) (42)
Vaccinia	(41) (37) (42)
PRD1 bacteriphage	(41) (22) (37) (42)
H5N1 avian influenza virus	(43) (37) (42)
MS2 Coliphage	(18) (22) (37) (42)
Poliovirus type 3	(18) (22) (41) (37) (42)
FUNGI, ALGAE, MOLD, YEAST	
Candida tropicalis	(6) (37)
Candida albicans	(6) (26) (30) (43) (41) (37) (42)
Mites	(29) (37) (42)
Aspergillus niger fungi	(43) (41) (37) (42)
Algae	(43) (9) (14) (24) (12) (37) (42)
Gliomastix cerealis	(41) (37) (42)
Epidermophyton sp.	(41) (37) (42)
Dreschslera australiensis	(41) (37) (42)
Chlorella vulgaris	(41) (37) (42)
Cladosporium cladosporioides	(41) (37) (42)
Candida pseudotropocalis	(41) (37) (42) (42)
Aureobasidium pullans	(41) (37) (42)
Aspergillus verrucaria	(41) (37) (42)
Aspergillus versicolor	(41) (37) (42)
Aspergillus terreus	(41) (37) (42)
Aspergillus sydowi	(41) (37) (42)
Gloeophyllum trabeum	(41) (37) (42)
Microsporum sp.	(41) (37) (42)
Microsporum audouinii	(41) (37) (42)
Monilia grisea	(41) (37) (42)
Oscillatoria	(41) (37) (42)

Penicillium chrysogenium	(41) (37) (42)
Pencillium commune	(41) (37) (42)
Penicillium finiculosum	(41) (37) (42)
Penicillium pinophiliumn	(41) (37) (42)
Penicillium variable	(41) (37) (42)
Phoma fimeti	(41) (37) (42)
Pithomyces chartarum	(41) (37) (42)
Poria placenta	(41) (37) (42)
Scenedesmus	(41) (37) (42)
Saccharonyces cerevisiae	(41) (37) (42)
Scolecobasidium humicola	(41) (37) (42)
Trichoderma viride	(41) (37) (42)
Trichophyton interdigitale	(41) (37) (42)
Trichophyton maidson	(41) (37) (42)
Trichophyton mentogrophytes	(41) (37) (42)
Trichophyton sp	(41) (37) (42)
Alterania alternate	(41) (37) (42)
Aphanizomenon sp .	(37) (42)
Aspergillus flavus	(41) (37) (42)
Chaetomium globosum fungi	(51)[1] (41) (37) (42)
Aureobasidium pullulans funi	(51)[1] (37) (42)
Trichoderma virens (fungi)	(51)[1] (37) (42)
PROTOZOA PARASITES	
Cryptosporidium parvum (oocysts)	(41) (42)
Giardia	(41) (42)
BIOFILMS	
Mixed biofilms	(6) (32)

Note: Not much is known about the effectiveness of QAS compounds on nonenveloped viruses, although some efficacy was observed against MS2 in solution. While a QAS concentration as low as 10^{-5} mol/l was observed to cause a 0.91 -log10 reduction of MS2, it remains unclear whether these results were from inactivation or aggregation (data not shown).(19)

7. TOXICOLOGICAL AND ENVIRONMENTAL ASPECTS

Based on the results of a degradation experiment in aerobic activated sludge, it was concluded that **Si-QAC was readily biodegradable** (after 6 days, 70% of the substance was degraded) (52) and is also expected to rapidly hydrolyze. (53)

The octanol–water partition coefficients (Kow) can be a measure of the extent to which a specific compound is taken up by organisms and is often a suitable parameter to compare different antimicrobial substances, particularly for organic compounds. Si-QAC has a bioaccumulation potential with a Kow of 2.9. (52) Substances with a Kow>3 are considered as substances that bioaccumulate because they are more likely to partition into lipids than to stay in the aqueous environment. (54) **Si-QAC can be considered within the safety range for bioaccumulation**.

Potential exposure routes include dermal, oral or inhalation pathways. Si-QAC compounds are considered safe. There is however evidence of **skin sensitization** for Si-QAC. (52)

Although Si-QAC is a corrosive chemical, **the USEPA does not expect any severe effects of Si-QAC use on human health**. (53), (55)

The QAS compound we used has been tested extensively and found to exhibit **low toxicity**.(22)

Mutagenicity and teratogenicity tests in albino rats were negative, and the LD50 was found to be 12.3 g/ kg body weight. (22)(56)

No cytotoxicity demonstrated in silicone rubber tracheoesophageal shunt prostheses application. (6)

8. DURABILITY

a) In textile applications, up to 20 industrial laundry cycles (16) or 10 washing cycles. (28)

b) At 25 and 50°C antibacterial coated cellulose membranes, polyvinyl alcohol membrane and glass showed stable antimicrobial activity and stable chemical bonding at pH values ranging from 1.5 to 10.1. At 90° C, stability was demonstrated for pH values of 3.6 to 5.8. (19)

c) High durability on silicone rubber. (6)

d) Durability of 5 months in undersea conditions (12)

8. UPDATE ON COVID-19[2]

"**Quaternary ammonium compounds are listed and recommended among the disinfectants against CoVID-19 by the United States Environmental Protection Agency (USEPA).** (57) Variations in the chain length, nuclear size, and basicity of the complex decide the antimicrobial potentiality. For instance, an increase in the chain length from C12eC16 show the greatest antimicrobial activity. These agents are membrane activating groups as they directly interact with the cytoplasmic membrane of bacteria and yeast. **The presence of long nonpolar tail makes them effective against a lipid-containing virus such as CoVID-19 (i.e., phospholipid layering)**. The long chain of hydrocarbon act as permeability enhancer that influences the surface-active properties whereas the cationic portion binds to negatively charged nucleic acids condensed inside the capsid leads to virucidal activity." (57)(58)

"**We postulate that QACs should be effective decreasing the viral load for disinfection procedures against COVID-19 as both contain relatively similar phospholipid bilayers**. Furthermore, a newer generation of multicationic QACs has recently been developed, which warrants further studies against these emerging viruses. These findings, coupled with the dangerous trend of inappropriately misusing disinfectants, warrants an urgent need to establish consistency in how we analyze the effectiveness of QACs against the family of coronaviruses to allow factual recommendations for use of disinfectants." (59)

"We propose that in particular, cetylpyridinium chloride is a simple molecule that is cheap, safe, clinically approved, widely accessible in hospitals and the consumer sector and which could enter clinical trials immediately. If reported to have activity in vitro against SARS-CoV-2 subsequent delivery in the form of a mouthwash or nasal spray containing this compound may be an effective way both to combat the virus at its point of entry and reduce SARS-CoV-2 transmission." (60)

"we provide definitive evidence of efficacy for inactivation of SARS-CoV-2, on contaminated prototypic HITES and suspensions, of products formulated with the following microbicidal actives: ethyl alcohol, para-chloro-meta-xylenol, salicylic acid, and quaternary ammonium compounds. All of the microbicidal actives were effective for inactivating SARS-CoV-2,

[2] No data are available on the specific compound dimethyloctadecyl(3(trimethoxysilyl)propyl)ammoniumchloride. However, general indications are provided for the class of compounds QACs

demonstrating ≥3.0 to ≥4.7 log10 reduction of infectious virus within the tested 1 to 5 minutes contact time in virucidal efficacy testing conducted per applicable ASTM International and EN standards." (61)

"QACs are attractive as they are relatively nontoxic, colorless, and odorless. They are well-known for inactivating enveloped viruses but their virucidal activity depends on concentration, duration of application, and temperature. Tsujimura et al. evaluated the virucidal effect of three QACs, namely benzalkonium chloride, (BZK), mono; bis (trimethyl ammonium methylene chloride)-alkyl (C9–15) toluene (MBAT), and didecyldimethyl ammonium chloride (DDA).
It is found that the QACs require warmer temperatures to exhibit more significant virucidal properties. The QACs at their highest recommended concentrations of 0.05% (w/v), 0.02% (w/v), and 0.02% (w/v), respectively, had no virucidal effect on enveloped equine herpesvirus type 1 after 10 min reaction time at 0◦C. When the temperature is increased to room temperature, the virucidal activity of the QACs is found to be dependent upon duration of reaction. Reaction times shorter than 1 min produced no virucidal effect, while the minimum effective concentration (MEC) at 5 min is mostly double that of the MEC for a 10 min reaction. MEC is defined as the lowest concentration of the biocide that reduced the virus titer value by 99.99% or greater as compared to control reactions. This suggests that effective disinfection utilizing QACs is best achieved using warm water and longer reaction times." (62)

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