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Quaternary Ammonium Compounds: Usage in Households during COVID-19 Pandemic, Boon, or Bane?

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Abstract

Quaternary ammonium compounds (QACs) have been used as disinfectants and as components in various household items since long. The furore and panic created during the COVID-19 pandemic triggered an unprecedented increase in their usage in health-care facilities as well as in households. This narrative attempts to explore the usage of various QACs in households during the pandemic and delve into the increased exposure and consequent health outcomes. A comprehensive literature search was performed on various databases to include the studies conducted on QACs since 2019. Multiple studies reported an increase in the exposure to QACs during the pandemic and this surge was reflected as adverse effects in human beings as well as the environment – cytological aberrations, intoxication, and damage to aquatic life being the main-stays.

Keywords: COVID-19, Disinfectants, Quaternary ammonium compounds, SARS-CoV-2.

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Background

COVID-19 is a respiratory viral disease spread by either droplet infection or through fomites of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] It was identified in Wuhan, China in December 2019, characterized by acute respiratory distress such as dry cough, body ache, and pneumonia. Declared a public health emergency on January 30, 2020 by the World Health Organization (WHO),[2] the pandemic ushered in the widespread usage of surface disinfectants and hand sanitizers to limit the transmission of the virus through fomites. There was recklessness in the way that these products were used during the lockdown period, especially in households with home isolations and home caregivers at peak during the first and second wave. There was also a shift from the previously used disinfectants toward the quaternary ammonium compounds (QACs) due to their less corrosive nature, as well as stability in a wider range of temperatures.[3]

A group of chemicals, QACs are present as an active ingredient in cleaning products for disinfection in health-care facilities and public places, where the risk of transmission of bacteria or viruses is relatively higher. The virucidal activity of QACs against SARS-CoV-2 limits the viral transmission through fomites.[4] However, their indiscriminate use in household premises is a cause for concern.

Historical Timelines

It was in 1916, that the Rockefeller Institute in New York, U.S.A first reported the bactericidal properties of quaternary ammonium salts, derivatives of hexamethylenetetramine. Their use as a germicide or disinfectant had to await formal recognition until 1935.[5] Benzalkonium chloride (BZK) was the first QAC to be introduced as an alternative to carbolic acid for skin antisepsis and scrubbing in the surgical setting. It showed such significant reduction in skin flora, that its role as a potential surface disinfectant was explored, which became a huge success.[6] Thereafter, there was a huge increase in the use of QACs consequent to the development of benzalkyl-dimethylammonium chloride, also known as benzalkonium chloride (ADBAC or BAC). By the year 1940, the use of QACs expanded and their use as surface-active disinfectants and detergents markedly increased.[7] However, their use as antiseptics and household disinfectants were banned in European countries, as a fall-out of their various side effects.

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Aim and Objective

This narrative has been done with the aim of exploring the various QACs that have been used as surface disinfectants in the household set-up in the backdrop of the COVID-19 pandemic with the objective of delving into the varied health outcomes and side effects, consequent to the exposure to QACs in households.

Methodology

This study has been done in a central government dental institute over a time span of 4 months. It is a narrative review based on a comprehensive literature search carried out on databases such as PubMed, LILACS, Cochrane Library, Public Health Electronic Library, TRoPHI, DoPHER, Medknow, and Google Scholar. Studies done

since 2019, mentioning the use of QACs as surface disinfectants in households were included in the study. For a broader perspective, studies advocating the effectiveness of QACs against SARS-CoV-2, laboratory-based studies, and survey-based research have also been included in the study.

Review of Literature

1. Zheng *et al.,* in August 2020, in Bloomington, U.S.A, evaluated the concentration of nineteen QACs in residential dust collected before and during the COVID-19 pandemic. It was found that the amount of QACs in the residential dust increased during the pandemic as compared to the dust collected before the pandemic. The most common QACs reported to be increased were benzyl alkyldimethyl ammonium compounds (BACs), dialkyl dimethyl ammonium compounds (DDACs), and alkyltrimethylammonium compounds (ATMACs) with 91%, 39%, and 38% changes, respectively. The overall increase in QACs was found to be 62%. This pointed to the fact that indoor exposure to QACs had become widespread and significantly higher in households with increased disinfecting frequencies during the pandemic.[8]
2. Babić *et al.,* in September 2020, in Croatia, reported the toxicological aspects of increased use of surface disinfectants during the pandemic. In 2019 and 2020, they reached out telephonically to people with suspected and symptomatic poisonings with disinfectants and compared the frequency of exposure. Most commonly, glutaraldehyde and BAC were reported as the active ingredients in disinfectants. It was found that the usage of disinfectants doubled in the first half of 2020. These findings confirmed the increased availability and usage of disinfectants that has probably led to its toxigenicity. Increased risk of poisoning were also evaluated, and pre-school children were concluded to be at higher risk.[9]
3. Li *et al.*, in December 2020, in Nevada, U.S.A, evaluated the risk of exposure to disinfectants used in the pandemic and the associated health risks. They studied 14 QACs used for surface disinfection and found that human exposure to QACs arises from the route of ingestion, thereby leading to intoxication. Children were found to have much more frequent surface-to-hand and hand-to-mouth contact than adults.[10]
4. Hrubec *et al.,* in March 2021, in Virginia, U.S.A, tested the accumulation potential of QACs in blood and their adverse effects. They studied the association between concentration of QACs in blood and their toxicological endpoints focusing on the statistical analysis of various health-related biomarkers of inflammation, mitochondrial function and sterol homeostasis. A clear dose-response relationship between QACs and blood concentrations of inflammatory markers, cholesterol synthesis intermediaries, and mitochondrial function was established. It was found that approximately 80% of the participants had QACs in detectable concentrations. Benzalkonium chloride was found to inhibit the Dhcr7 gene, responsible for providing instructions to make 7-dehydrocholesterol reductase which plays a role in cholesterol production. Therefore, exposure to these compounds in developmental stages can be a major risk factor in the pathogenesis of developmental disorders. The study had a smaller sample size which necessitates future research in the area on a larger scale with long-term observation times.[11]
5. Kreipe *et al.*, in August 2021, in Göttingen, Germany, performed a retrospective analysis of 145 patients with complaints of contact sensitization to disinfectants. It was noteworthy that only five patients had reacted positively at a higher concentration of 0.05%, as compared to a lower concentration of 0.03% in the patch test. No signs and symptoms were associated with the patch test at these concentrations; therefore, all patch tests were proved to be of no clinical relevance.[12]
6. Guo *et al.*, in October 2021, in Wuhan, China, conducted a questionnaire-based survey to investigate the impact of the COVID-19 outbreak on consumption of household disinfectants and the extent of their usage. The questionnaire was designed based on the information about the environmental risks of disinfectants and expertise from the Ecopharmacovigilance department. The frequency of usage of household disinfectant products before the outbreak and at the time of survey was evaluated. It was observed that 37.3% of respondents had used household disinfectant products occasionally and only 3.6% had disinfected their home environment every day before the outbreak. However, during the COVID-19 outbreak, 26.2% of respondents used household disinfectant products for disinfection in their homes on a daily basis. Thus, the increase in usage of disinfectants for household disinfection was found to be significantly high. In addition, the perception of the public regarding the relation between environmental impacts and practice of disinfectants was found to be low. Less than half of the respondents reported a positive attitude toward the source control of pollution by disinfectants. The findings of this survey raise additional concerns about the use of household disinfectant products, particularly in light of the potential health risks.[13]
7. Zheng *et al.,* in November 2021, in Bloomington, U.S.A, demonstrated the presence of eighteen QAC in blood samples. The blood samples were collected during two distinct periods, before the outbreak of the COVID-19 pandemic, in 2019, from February to August, and during the pandemic in 2020, from April to August. The ΣQAC concentration, 6.04 ng/ml, was significantly higher in samples collected during the pandemic than in those collected before, which was 3.41 ng/ml. Moreover, the *in vivo* clearance rate of QACs in the liver was found to be lower, thus suggesting a higher bio-accumulation. This was linked most likely due to the widespread use of QACs during the pandemic. However, the study did not mention any biochemical alterations in the body tissues. The results of this study provide an important insight into the human hepatic bio-transformation and first bio-monitoring data for three QAC groups as well as providing a basis for future epidemiological studies. However, the study does not provide information on the use of disinfectants in participants' homes. Therefore, a direct link between the increased use of disinfectants in households and elevated levels of QACs in blood could not be established.[14]
8. Alygizakis *et al.,* in a study in Greece, in December 2021,using liquid chromatography–mass spectrometry, reported the presence of chemical compounds in influent wastewater before and during the COVID-19 pandemic. During the lockdown conditions, the concentration of cationic quaternary ammonium surfactant increased by 331% with Benzalkonium chloride, Alkyltrimethylammonium halide,

and Dimethyl Tetradecyl Ammonium Bromide having the highest concentrations. Furthermore, six compounds of alkyltrimethylammonium chlorides (ATMAC) and diallyldimethylammonium chloride (DADMAC), that is, ATMAC-14, ATMAC-16, ATMAC-20, ATMAC-22, ATMAC-13/DADMAC-4:10, and DADMAC-8:10 were identified only during the pandemic. However, this study did not provide any health implications of the increase in the concentration of chemicals in wastewater.[15]

QACs: Chemical Composition and Mechanism of Action

QACs are cationic surface-active agents with a central nitrogen atom and four attached functional groups which play a major role in their classification and antimicrobial activity [Figure 1].

They target the cell membranes of microbes, thereby inactivating them. Being hydrophobic in nature, they can potentially act against lipid-containing enveloped viruses such as the SARS-CoV-2 virus.[16]

Classification

There are seven generations of QACs, which have been classified on the basis of providing enhancements and toxicity. These are shown in Table 1.[17]

QACs in the Household: The Types[18]

The most common types of QACs used in various household items are BAC, DDAC, ADBAC, cetylpyridinium chloride (CPC), and cetrimonium chloride [Table 2].

Disinfectants during the COVID-19 Pandemic: Guidelines for Usage

With the advent of COVID-19 pandemic, guidelines were issued by the WHO, CDC, and the US-Environmental Protection Agency (US-EPA) regarding the use of surface disinfectants against SARS-CoV-2. These are as follows:

WHO guidelines

Certain high-touch surfaces in non-health-care settings have been identified by the WHO for priority disinfection. These are doors and window handles, kitchen and food preparation areas, countertops, bathroom surfaces, toilets, taps, touchscreen personal devices, personal computer keyboards, and work surfaces. Wiping of surfaces by cloth or wipe soaked in the disinfectant has been recommended, but not spraying.[19]

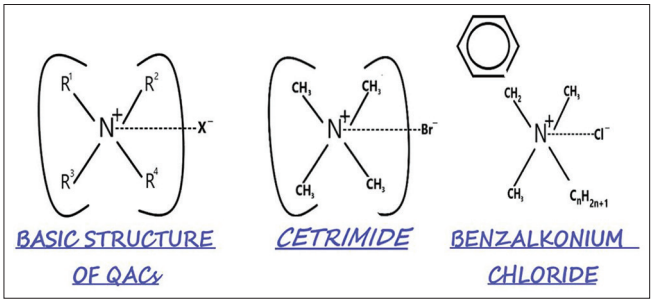

Figure 1: Chemical structure of quaternary ammonium compound and its derivatives

CDC guidelines

Disinfection of homes during the pandemic has been recommended by the CDC, in the eventuality of someone falling sick or tested positive for COVID-19 and being at home for the past 24 h. For dilution of QACs, water at room temperature has been recommended. Eating, drinking, and breathing (without masks) in the area of usage of QACs or injecting the cleaning and disinfection products into the body or their application directly on to the skin is to be avoided due to potential side effects. The use of surface cleaning and disinfection products for wiping or bathing people or pets is also not recommended.[20]

US-EPA guidelines

These guidelines advise the use of only those disinfectants listed under EPA List: N and deemed to be effective against COVID-19. Out of 594 products listed as disinfectants in the U.S-EPA List N: for the use against SARS-CoV-2, 275 of them contain QAC as the active ingredient.[20] QACs in the EPA list can be used with dilutable formulations, and a varying contact time of 1–10 min. Bleach solutions can be used as a substitute if found appropriate for the surface in case of non-availability of EPA listed products.[21]

QACs: Uses and Permissible Concentrations[22-24]

QACs such as BAC, DDAC, alkyl-dimethyl-benzyl-ammonium-saccharinate (ADBAS), and CPC find their use as ingredients in an array of household surface disinfection products. They have a wide range of uses as denoted below:

- BACs are commonly used disinfectants and sanitizers at homes, schools, hospitals, and restaurants to eliminate or reduce the spread of pathogens and other harmful microorganisms on surfaces and in the air.
- For indoor and outdoor hard surfaces, utensils, laundry, carpets, swimming-pools, decorative ponds, and re-circulating cooling water systems, a quaternary ammonium biocide is used.
- They are often present as active ingredients and are used in combination with other chemicals in antibacterial sanitizing hand rubs, antimicrobial soaps, skin cleansers, food preservatives, toothpaste, shampoos, and other products for other surfaces.
- Used in a variety of agricultural, clinical, and industrial applications such as paints and coatings, adhesives, sealants, and pesticide, they are also used in a myriad of domestic applications including fabric softeners, personal hygiene, and cosmetic products such as shampoos, lotions, ophthalmic solutions, medications with nasal route of delivery and in industrial applications such as paints and coatings, adhesives, sealants, and pesticides.
- They have been shown to have greater antimicrobial activity than conventional surfactants such as sodium lauryl sulfate, depending on the concentration and duration of exposure.

The permissible concentrations for BACs are as follows:

- Food products: Europe Regulation: 0.1 mg/kg.
- Food samples: Up To 14.4 mg/kg.
- Hair conditioners: 0.5–2%.

Table 1: Classification of QACs

S. No	*Generation*	*Names*	*Composition*	*Activity*	*Example*
1.	1st	Benzalkonium chlorides	Benzalkonium chloride with variation in the number of carbon of the alkyl chain	Lowest relative biocidal activity, used as preservatives	Benzalkonium chloride
2.	2nd	Substituted benzalkonium chlorides	Substitution of the aromatic ring hydrogen with chlorine, methyl, and ethyl groups	High biocidal activity	Alkyl-dimethyl benzyl ammonium chloride
3.	3rd	Dual QACs	Combination of two specific QACs	Increased biocidal activity. Stronger detergency. Relative lower toxicity Increased safety to the user	Equal mixture of alkyl-dimethyl benzyl- ammonium chloride and alkyl- dimethyl-ethyl benzyl-ammonium chloride
4.	4rth	Twin or dual chain QACs	Dialkyl-methyl amines	Superior germicidal performance, lower foaming. Greater tolerance to protein loads and hard water	Didecyl-dimethyl ammonium chloride Dioctyl-dimethyl ammonium chloride
5.	5th	Combination of fourth with second generation QACs	-	Outstanding germicidal performance .Active under more hostile conditions. Safer to use	Didecyl-dimethylammonium chloride Alkyl - dimethyl benzyl ammonium chloride
6.	6th	Polymeric quaternary ammonium chlorides	-	-	-
7.	7 th	Bis-quaternary ammonium chlorides with polymeric quaternary ammonium chlorides	-	-	-

Table 2: Active ingredients in common commercially available disinfectants

S. No.	*Name*	*Active ingredients*	*Uses*
1.	Clorox	ADBAC, C12-C16 ADBAC, alkyl-dimethyl- ammonium chlorides and isopropyl alcohol	As wipes, cleaning gels, and as many other cleansing products
2.	Dettol disinfectant spray	Ammonium compounds, BAC, and saccharinate	For disinfecting hard and soft surfaces in homes, against several microbes, and viruses including SARS-CoV-2
3.	D-256	10.14% didecyl dimethyl ammonium chloride, 6.76% Alkyl (50% C14, 40% C12, and 10% C16) dimethyl benzyl ammonium chloride	In healthcare facilities such as hospitals, nursing homes, laboratories, for surface disinfection of walls, floors, hospital beds, tables, chairs, trolleys, stretcher, hospital furniture, and patient care items
4.	Lysol	0.10% Alkyl-dimethyl benzyl ammonium – saccharinate (50% C14, 40% C12, 10% C16) and 58.00% ethanol	For disinfecting frequently used surfaces, light switches, door handles, kitchen counters, and remotes

- Mosquitocide: 200 ppm.
- Disinfectant (marketed as lysol): 0.1% (w/v).

QACs: Advantages[3,25]

1. Effective as a single-component microbial biocide in the mitigation of 37 of the top 50 organisms found on the CDC's list of micro-organisms most commonly found healthcare-acquired infections like MRSA, adenovirus, and many more. Broad-spectrum antimicrobial activity.
2. Stable in direct sunlight when kept in glass packaging.
3. Do not generate odor.
4. Are non-corrosive.
5. Have a shelf-life >3 years.
6. Do not damage clothing and carpets.
7. Are biodegradable.
8. Are effective cleaners.
9. Are non-corrosive to metal pipes or equipment, do not tarnish silver, and are much less harsh on the skin than traditional disinfectants.

QACs: Disadvantages and Adverse Effects[26]

Despite their multifold advantages, QACs also have some downsides, as depicted below:

- Cannot be diluted in hard water.
- Tend to cling to surfaces, making them difficult to rinse off, and resulting in possible taint problems.
- May cause irritation of the nasal passages and eyes when used in nasal sprays and eye drops. This can trigger rhinitis and keratitis, respectively.
- Not as effective as other disinfectants at physically bonding with the textile, resulting in a rapid concentration decrease in the textile.
- Can cause burns to the skin and mucous membranes in their non-diluted form.

- Inactivated at low pH and by salts such as calcium and magnesium.
- Cause serious anti-microbial resistance.

Many adverse effects are propagated due to the irrational use of QACs such as:

1. Damage to aquatic life: Most QACs after usage, enter wastewater treatment plants (WWTPs). The concentrations of QACs detected worldwide in surface water and wastewater effluent usually range from <1 μg/L to approximately 60 μg/L. However, recently QACs have been found to be up to 10 times more concentrated in treated effluent than influent wastewater.[27] These are toxic to aquatic organisms such as fish, daphnids, rotifer, algae, protozoan, and many other microorganisms.[28]
2. Dermal effects: BAC, a common ingredient in many household disinfectants, topical skin cleansers, and household laundry rinse aids has been implicated in causing contact dermatitis and granular parakeratosis. People with minimum exposure to BAC showed less severe symptoms of granular parakeratosis as compared to those who were exposed chronically.[29] QACs such as DDAC and ADBAC, depending on the concentration, can be irritant to both skin and eyes and were shown to cause dermal and ocular irritation. Many commercially available diluted products are also labeled as dermal irritants and it is advised to avoid their contact with eyes, skin, or clothing.[30]
3. Respiratory effects: Symptoms of exposure to QACs have been also reported to be on lungs. Studies have established that irritation due to chronic exposure to QAC leads to sensitization and increased risk for asthma or other respiratory disorders such as chronic obstructive pulmonary diseases (COPD). A significant increase in the risk of asthma and nasal symptoms at work has been reported.[31,32] As QAC is not volatile, it is believed to be not associated with higher risk, but the literature has provided us with the reports of nursing professionals being more prone to certain nasal symptoms and physician diagnosed asthma. Furthermore, major health risks were attributed to those who are involved in the dilution of QACs.[33,34]
4. Cellular changes: Measurable concentrations of QACs have been found in the blood that have resulted in cellular disruption, mitochondrial dysfunction, alterations in cholesterol synthesis, and presence of inflammatory markers.[11] Mitochondrial fragmentation was also reported due to toxicity of Alkyl-N,N,N-trimethylammonium and this results in reduced cellular energy charges.[35] Adverse influences are also seen in cholesterol biosynthesis and estrogen signaling, thereby having deleterious effects on embryonic development.[36]
5. Antimicrobial resistance: The excessive use in household and industrial products has led to concerns about the rise in antimicrobial resistance in engineered and natural systems.[37] Injudicious use of QACs can lead to the development of antimicrobial resistance which is recognized by the WHO as one of the ten global threats to humanity.[38]

Discussion

The COVID-19 pandemic brought significant changes in consumer behavior and needs with regard to use of disinfectants. The entire world turned to preventive practices such as hand hygiene, respiratory etiquettes, and above all, the use of surface disinfectants. Among the most significant actions taken by governments was the issuance of guidelines for the public on disinfection practices of their homes to reduce the risk of exposure to the virus. QACs were listed for use against SARS-CoV-2 in the US-EDP list which highlighted their significance across all sectors, from health-care facilities to households. The establishment of the virucidal efficacy of QACs against SARS-CoV-2 on treated surfaces in 2021, led to the decrease in communicability and fomite transmission of SARS-CoV-2.[39] This also led to the widespread use of QACs in households, workplaces, and industry and an exponential increase in demand for health and hygiene products, more so, disinfectants as also hand sanitizers. The non-inflammable nature and relatively shorter contact time of 15–30 s even in the presence of mucin, bovine serum albumin, and hard water makes them a good choice as disinfectants with good compliance.[40] However, efficacy of QACs against the SARS-CoV-2 still remains the focus of an ongoing area of active research and therefore, their usage has to be guided by justified need, adequate caution, and wisdom. Studies in India are also required to generate data on knowledge, attitude, and awareness regarding QACs and their long-term and immediate health outcomes.

Various generation changes were brought about in QACs, based mainly on the union and modification of chemical components for better biocidal and virucidal effect and safety record. The fifth-generation, consisting of ADBAC with DDAC, has been found to be more effective against viruses, including SARS-CoV-2 in comparison to other QACs, which are more bactericidal.[41] Being in the early stages of development, further evidence-based research is required to identify the best generation changes and combinations for different requirements. A myriad of health hazards have been shown to be associated with the use of QACs, such as reproductive disorders, respiratory illness such as asthma or chronic obstructive lung diseases, central nervous system impairment, and developmental defects. The most prominent adverse reaction is the local irritation on contact with the eye or skin.[42] All these may be just the tip of the iceberg.

Limitations of the Study

The presence of heterogeneity across included studies with reference to their study design and measures of outcome made it difficult for assessment of available data objectively. Only published studies were included which could lead to overestimation of positive results. Few studies reported an increase in the use of QAC-based surface disinfectant; however, its direct correlation with the health or environmental hazards was not estimated during the COVID-19 pandemic. Future studies evaluating the immediate and long-term health outcomes due to increased use of QACs in the COVID-19 pandemic are recommended. Information and educational material are required to create awareness among the public regarding correct and appropriate usage of surface disinfectants in households.

Conclusion

QACs have been a boon during the pandemic in preventing the transmission of SARS-Co-V-2 in health-care facilities as well as in households. The households became the primary health-care facilities by dire necessity, during the various waves of the pandemic. Many guidelines and safety protocols have been released for the directions of their usage, but the literature

regarding its potential hazards is still not prominent. It would be wise to use QACs only after identifying the risk of transmission and also with due precautions, namely, wearing mask and gloves to prevent respiratory and skin exposures and future adverse outcomes. COVID-appropriate behavior such as hand hygiene and use of mask should be diligently followed to limit the spread of coronavirus rather than the indulgent use of disinfectants. Let, use of QACs remains a boon, not bane.

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