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MINI REVIEW

Chronic quaternary ammonium compound exposure during the COVID-19 pandemic and the impact on human health

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Abstract

Objective This review examines a relevant, and underacknowledged, emerging global public health concern—the widespread exposure to quaternary ammonium compounds (QACs) during the COVID-19 pandemic. QACs are a widely used class of cationic surfactants with broad spectrum antimicrobial activity that serve as the active ingredients in antimicrobial products. While these compounds have been used for decades, the production and consumer use of QAC-containing products have steeply risen during the COVID-19 pandemic to control and prevent the spread of the SARS-Cov-2 virus. As a result, human exposure to QACs has also drastically increased.

Methods This critical review was conducted by searching the key terms "quaternary ammonium compounds," "disinfectants," "COVID-19," "SARS-Cov-2," "human health," and "human exposure" in the major search engines, including Google Scholar, PubMed and Science Direct.

Results QACs are generally considered safe and effective, yet the magnitude of QAC exposure and the subsequent health effects have not been adequately investigated. Recent studies have revealed the potential for bioaccumulation of QACs in blood and tissue. Inhalation and dermal absorption of QACs are identified as the most significant exposure routes for adults, while children and infants may be significantly more vulnerable to QAC exposure and potential adverse health effects.

Conclusions QACs are an important tool to protect individual and public health, but understanding the impact of widespread QAC exposure is vital to guide best practices for QAC use and minimize the associated health risks. These pandemic era results warrant further investigation and raise additional questions about the short-term and long-term health effects of chronic QAC exposure.

Clinical trial registration Not applicable.

Keywords Quaternary ammonium compounds · Disinfectants · COVID-19 · Human health · Exposure

Introduction

The use of disinfectants and sanitizers is a common practice in homes, workplaces, schools, industries, and hospitals. Quaternary ammonium compounds (QACs) are a large group of positively charged polyatomic ions with broad-spectrum antimicrobial activity that are highly soluble in water and various organic solvents [1]. Accordingly, QACs are frequently used as the active ingredients in many antimicrobial products. The most commonly used QACs in disinfectants and cleaners are benzalkonium chlorides (BACs), alkyltrimethylammonium chlorides (ATMACs), and dialkyl dimethyl ammonium chlorides (DDACs) [1]. While approximately 80% of commercial QAC-containing products are biocides and cleaning agents, QACs are also used in shampoos, conditioners cosmetics, lotions, mouthwash, deodorizers, and laundry products [2]. According to the CDC, end-use QAC concentrations are typically between 0.05 and 0.2% and generally require 10 min to achieve disinfection. QACs are relatively stable compounds that remain active on surfaces for several hours after application [3].

In 2020, the CDC listed QACs on the Environmental Protection Agency (EPA)'s List N Disinfectants, which identifies products that meet the EPA's criteria to use against SARS-CoV-2 [4]. Of the 500+ products on the EPA's List N: Disinfectants for Coronavirus (COVID-19), nearly half

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contain QACs as the active ingredients. The production of QAC-containing products has risen drastically during the COVID-19 pandemic and is forecasted to continue to increase over the next decade [2]. Thus, considering the prolific use of these disinfectants, sanitizers, and QACs-containing products, humans are extensively and repeatedly exposed to QACs, and at levels higher than previously expected.

Human exposure to QACs is likely to occur via three routes of entry: dermal contact with QAC-containing products and QAC-treated surfaces, inhalation of aerosolized droplets from cleaning sprays and QACs adhered to dust particles, and ingestion of food and water sources. Yet, while exposure to QAC-containing products is widespread and expected to increase in the years to come, the extent of QAC exposure during the pandemic and the health effects of chronic QAC exposure are largely unknown. This work will discuss limitations in QAC toxicity and risk assessment practices, review recent pandemic era data evaluating QAC exposure and associated health effects, as well as identify knowledge gaps in our understanding of the long-term impact of QAC use.

Methods

This critical review was conducted by searching the key terms "quaternary ammonium compounds," "disinfectants," "COVID-19," "SARS-Cov-2," "human health," and "human exposure" in the major search engines, including Google Scholar, PubMed and Science Direct. Search results were reviewed, and the studies published since 2020 examining human exposure to quaternary ammonium compounds were included in the results and discussion. For a broader perspective, background studies evaluating QAC toxicity, occupational exposure, and the association between QAC use and the development of antimicrobial tolerance are discussed.

Results and discussion

Evaluating the toxicity of QAC disinfectants

In the USA, the EPA is responsible for registering antimicrobial pesticides. QACs were first registered in the USA in 1947 and have been one of the longest used active ingredients in disinfectants and cleaning products. There are approximately 10,000 registered QAC formulations, and the EPA has clustered QACs into four groups for testing purposes [5]. EPA requirements for experimental toxicology data include identifying a maximum permissible level that meets the reasonable certainty of no harm standard [6, 7]. Nevertheless, recent evidence suggests that more than half of QAC-containing cosmetics and personal care products contain concentrations of QACs that exceed the recommended and permissible concentrations [8]. To support QAC product registration, regulatory studies have shown that single dose administrations of QACs led to nearly 99% of QACs being eliminated via feces and urine, while less than 1% was retained in tissues [9]; however, more recent results have indicated that the major excretory route for QACs is via bile into feces, which implies substantial intestinal absorption [10, 11]. Furthermore, while only a fraction of administered QACs were detected in tissues following the single dose administrations [10], these studies have not assessed bioaccumulation following repeated exposure or chronic low-dose exposure.

A notable limitation to previous toxicological data is that these assessments are largely unpublished company or regulatory reports that are conducted on individual QACs, yet most commercial QAC-containing products contain mixtures of compounds [12, 13]. During the production of QACs, mixtures of compounds with various alkyl lengths are produced and the precise composition of the mixture may never be adequately evaluated. It should also be considered that, while risk assessments generally assume additive effects of compounds, available toxicity data suggest that many toxicant mixtures, including QACs, do not demonstrate additivity [10, 14, 15]. These concerns highlight the importance of evaluating the composition and toxicity of the mixture, as well as considering the effects of frequent and/or multiple exposures, as in the case of healthcare or custodial workers.

QAC Exposure during the COVID-19 pandemic

Numerous studies and review articles have investigated the environmental fate and ecological impact of QACs and have identified biocide contamination as a worldwide environmental concern [1, 16]. Both BACs and DDACs have long been designated by the EPA as high production volume chemicals and are expected to increase by at least 10% in the next 5 years [17]. Likewise, many recent studies have identified an increased presence of QACs in the environment, including surface water, sediment, and soil, as well as fruits and dairy products; however, QAC concentrations generally do not exceed the acceptable daily intake of 0.1 mg/kg [18, 19]. In contrast, strikingly high concentrations of QACs have been identified in aquatic organisms, suggesting the potential for bioaccumulation [1, 20].

The Centers for Disease Control and Prevention's website "Cleaning and Disinfecting your Facility" states "the virus that causes COVID-19 can land on surfaces. It is possible for people to become infected if they touch those surfaces and then, touch their nose, mouth, or eyes. Disinfecting using US Environmental Protection Agency (EPA)'s List N disinfectants kills any remaining germs on surfaces, which further reduces any risk of spreading infection." CDC recommends, with precautions, daily cleaning for low-risk spaces, but advises more frequent cleanings in high trafficked, poorly ventilated, and high-risk shared spaces [21]. Consistent with public health recommendations for increased cleaning, 2020 survey results indicate that more than 70% households increased the frequency of cleaning and disinfection during the COVID-19 pandemic, and 80% of the households reported routinely using QAC-containing cleaning products [22]. Unfortunately, more than one-third of households use cleaners and disinfectants unsafely [23]. These unsafe, high-risk practices include direct application of disinfectants to skin or food, as well as direct inhalation or ingestion of these products, and are associated with adverse health effects [23, 24].

In accordance with the increased use and misuse of household cleaning products, accidental exposures to high concentrations of QAC-containing products have been recently documented. Comparing data from the National Poison Data System from January through March of 2019 and 2020, National Poison Control Centers received a 16.4% increase in calls related to disinfectant exposures and 20.4% increase in calls related to exposures to cleaning products in 2020 [25]. This study released on April 20, 2020, on the CDC's *Morbidity and Mortality Weekly Report*, identified exposure to QAC disinfectants and hand sanitizers as the predominant reason for the increase in calls. Ingestion of disinfectant was reported to be the most common exposure route, while inhalation was identified as the exposure route with the greatest percentage increase from 2019 to 2020. Published state data also exemplified this trend—comparing the same time period from 2019 to 2020, Michigan Poison Centers reported that the number of exposure calls related to disinfectants increased by 42.8%. Exposure occurred in the home for over 94% of calls [26]. Similar data have been reported internationally [27, 28], which further validates the growing global health concern.

Given that national and international regulatory agencies have long deemed QACs safe, effective, and not systemically toxic [13, 29], little is known about the magnitude and extent of QAC exposure with proper use of QAC-containing disinfectants. Human exposure to QACs during and after proper use of disinfectant and cleaners can occur via three primary routes of entry–dermal absorption, inhalation of indoor air, and mouth-mediated ingestion. Li et al. (2020) estimated the contribution of each route of entry to aggregate QAC exposure. Interestingly, dermal absorption due to proper handwashing did not lead to significant dermal uptake [30]. During handwashing, exposure to these compounds is limited to the approximate 20 s of recommended contact time and then, rinsed off. In contrast, it is predicted that dermal absorption following proper application of QAC products to hard surfaces is up to seven magnitudes higher than handwashing, and significantly above the maximum acceptable dose [30]. Once applied to hard surfaces, QAC residue can remain on the disinfected objects, surfaces, or adsorbed to solid airborne particles until it is wiped or rubbed off. An analysis of 22 disinfecting agents indicates that human exposure to QACs is significantly higher than exposure to other common cleaning product active ingredients in this surface application scenario [30], which further distinguishes QACs as potential ubiquitous indoor contaminants.

Dust in indoor environments is recognized as a significant reservoir for environmental contaminants, and QACs easily adhere to dust and solid indoor air particles. Inhalation of these particles is recognized as a major human exposure pathway [31]. Depending on the mode of application and frequency of disinfection, aerosolized QACs can quickly contaminate indoor environments [32]. Accordingly, Zheng et al. (2020) found that QAC concentrations were significantly higher in residential dust collected during the pandemic (2020), as compared to before the pandemic (2019). QACs were detected in more than 90% of samples, with the greatest increase detected for C12 and C14 BACs [22]. Overall, the total concentration of QACs in dust collected during the pandemic was greater than 60% more than samples collected in 2019 [22], suggesting that QAC inhalation has also likely increased during the pandemic.

There are limited studies investigating the health effects of chronic, low-level QAC exposure. Previous toxicity studies indicated that the high-water solubility of QACs would limit the ability of these compounds to bioaccumulate [13]. However, recent studies have demonstrated that particular QAC compounds are more likely to bioaccumulate and potentially contribute to adverse human health outcomes. Zheng et al. (2021) compared blood samples from 222 individuals, before and during the COVID-19 pandemic (in 2019 and 2020, respectively), and found that the total QAC concentration in blood was more than two-fold higher in samples collected in 2020 [33]. The most common QACs detected in blood were C12 and C14 BACs and C14 ATMAC, which were found in greater than 94% of pandemic samples. Importantly, QAC bioaccumulation potentials were determined and, corresponding to the blood concentrations, C12 homologs demonstrated the slowest clearance rates, indicating that these QACs could preferentially bioaccumulate [33]. A 2021 study by Hrubec et al. found that more than 80% of sampled individuals ($n = 43$) contained QACs in their blood, with preferential accumulation of C12 and C14 QAC compounds. These blood QAC concentrations were also correlated with biomarkers of inflammation, mitochondrial dysfunction and sterol imbalance [10]. Taken together, these pandemic era studies identify widespread QAC exposure, bioaccumulation and associated adverse health effects that necessitate further investigation.

Children and QAC exposure

Like adults, inhaled dust is a significant route of QAC exposure and entry for children [30]. Zheng et al. (2020) determined that the estimated daily intake (EDI) of ingested QACs adhered to indoor airborne particles is more than 10 times greater in children than adults living in the same household [33]. This difference is even greater for young children in households with higher disinfecting frequencies (1–5 times per week). While the EDI values in these scenarios were below the daily maximum acceptable levels, the estimates do not consider the potential consequences of bioaccumulation. Furthermore, these EDIs for household environments may not be transferrable to other indoor settings. More intense disinfecting protocols and frequencies have been recommended for daycare facilities, schools, gymnasiums, etc., than the average household. To evaluate QAC exposure in K-8 primary schools, Boles et al. sampled and assessed hard surfaces and air over three consecutive days in 2021. Each QAC listed in the product safety data sheets was detectable on desk surfaces and QAC concentrations significantly increased over the course of the three-day study [34]. As a result, daily QAC intake values may be significantly underestimated, particularly for children.

Due to characteristically low volatility, as compared to other active ingredients in non-QAC-based disinfectants and cleaning products, QACs are readily transferred from treated surfaces and objects to hands. As a result, mouth-mediated ingestion, due to hand-to-mouth transfer, accounts for a significant percentage of human exposure [30]. Given that children have substantially higher hand-to-mouth and object-to-mouth exposure, Li et al. (2020) estimated that mouth-mediated ingestion of QACs is up to 55 times greater in three-year-old children, as compared to adults [30]. Daycares, schools and recreational facilities, that are encouraged to frequently clean and disinfect items and spaces, are therefore areas that may pose the greatest risk for QAC exposure for this vulnerable and high-risk population.

Considering the evidence, QAC uptake is estimated to be at least one order of magnitude higher in children, as compared to adults, even in the same household [30]. Due to their small body weight and rapid growth and development, it is well recognized that infants are more vulnerable to the associated adverse health effects of environmental toxicants, and breastfeeding is considered a significant exposure route [35]. Zheng et al. (2022) have recently investigated the QAC concentration in breastmilk and estimated the daily intake of these compounds in breastfed infants. While less than half of the 48 mothers in the study reported that they regularly used QAC-containing disinfectant products in their homes, QACs were detected in all breastmilk samples [36]. Consistent with other studies, C14 BAC was the most abundant QAC detected in breastmilk. Lactational EDIs for QACs were found to decrease with increasing age and body weight, with the highest EDI for infants less than one month old, followed by 1–3 months, 3–6 months and 6–12-month-old infants. By comparing the median total QAC concentrations to other environmental contaminants, the authors conclude that QACs may accumulate in breastmilk at comparable or higher levels than other ubiquitous toxicants [36]. Lastly, early evidence from Herron et al. alarmingly suggests that BACs do cross the blood placental barrier, as well as the embryonic blood–brain barrier, where they can accumulate in neonatal brain tissue [37]. Cell culture and in vivo animal studies demonstrated that in utero exposure to BACs adversely affects early neurodevelopment [37]. Although preliminary, these results stress the importance of understanding the effects of in utero exposure to QACs and the potential developmental outcomes.

Future directions in QAC research

QACs are highly effective antimicrobial compounds and the public health benefits of using these products to control microbial pathogens and viruses, including SARS-CoV-2, cannot be underscored. Yet, the recent results discussed here bring the concern of QAC exposure, bioaccumulation, and the potential health risks to the forefront. The few human studies were based on a limited sample size, lacked demographic information, and were not paired samples across the time of investigation. It also cannot be assumed that the presence of environmental chemicals in blood, serum, urine, or tissues leads to adverse health effects, as toxicity depends on several factors [38]. CDC also advises that when interpreting data, blood levels of environmental chemical should not be confused with levels detected in the environment [38]. Furthermore, the few studies that have analyzed both toxicological data and bioactivity data have not observed strong associations [30]. However, the potential that these results translate to the population at large highlights a significant and extensive emerging public health concern that is currently underestimated. Insufficient data and methodological limitations support the call for additional studies to investigate the health effects and impact of chronic QAC exposure.

While these pandemic era results reveal widespread QAC exposure, they likely also underestimate occupational exposure, particularly for healthcare, sanitation and childcare workers. These highly exposed populations include those workers responsible for actively and routinely using QAC disinfectants. Frequent primary exposures are substantially greater than the secondary exposures common for other individuals in households, workplaces and public settings. Pre-pandemic case studies have suggested that acute exposure to QACs can cause irritant and allergic contact dermatitis and contribute to the development of occupational asthma [39–42]. A multi-year study from 2009–2015 identified regular QAC-disinfectant use by female nurses as a major risk factor for developing COPD [43]. However, despite these results, long-term occupational QAC exposure has been largely overlooked and is difficult to investigate, and occupational exposure limits (OELs) have not been set for QAC-containing disinfectants [44]. Dotson et al. (2020) recently established a framework to develop QAC OELs and determined 0.1 mg/m^3 to be the highest permissible QAC exposure limit for an eight-hour workday [45]. Although this case study was prompted by the increased occupational use of QACs during the COVID-19 pandemic, the determination of the potential OEL was predominantly based on pre-pandemic data and assumed all QACs are equally potent [45]. While this preliminary work may serve as a basis for future analyses, additional large-scale studies assessing occupational QAC exposure in various workplace settings are needed to adequately evaluate occupational risk and set protective guidelines and OELs.

Although antimicrobial efficacy testing was not discussed here at length, evidence suggests that commercial QAC-containing cleaning products use higher concentrations of active ingredients than are actually required to achieve the desired 99.9 efficacy, and most cosmetic and personal care products exceed the recommend levels of QACs [8, 46]. Recent experimental data evaluating the antimicrobial and viricidal activity of commercial cleaning products indicate that efficacy testing should be conducted at lower concentrations to avoid the deleterious health and environmental effects [46]. Critical analyses from 2020 have even raised questions about the relative efficacy of BACs against coronaviruses [47]. Likewise, results from the biomonitoring studies indicate that certain QACs, such as C14 and C12 homologs, are more likely to bioaccumulate [33]. Continued investigation into the associated health effects of bioaccumulation is warranted, and reevaluating the formulation and concentration of QAC mixtures to reduce potential bioaccumulation while maintaining efficacy is imperative.

Alternatively, while overuse of QACs and bioaccumulation are prominent concerns, chronic exposure to sublethal concentrations of QACs may alter the microbial communities that the cleaning product is intended to target and eliminate [48]. The effective dose of any biocide depends on the formulation, environmental surfaces, temperature and contact time [46, 47]. Since the antimicrobial mechanism of QAC action is dependent on cell lysis, sublethal concentrations do not induce bacterial cell lysis and thus, provide an opportunity for resistance to develop. Dozens of outbreaks have been documented and attributed to infections by disinfectant-resistant pathogens that have contaminated antiseptic products [49]. Furthermore, prolonged exposure to sublethal concentrations of QACs may select for QAC-tolerant organisms and therefore, simultaneously increase the abundance antibiotic-resistant organisms [50]. Antibiotic-resistant infections cause millions of fatalities annually and are recognized as a world health concern. Previous studies have indicated that QAC disinfectants can promote antibiotic resistance in opportunistic pathogens, *S. aureus* and *P. aeruginosa*, in hospital and community settings, as well as environmental bacteria in wastewater treatment plants [51–53]. Due to the widespread use during the COVID-19 pandemic, QACs have been identified as an emerging and significant cause of bacterial resistance to disinfectants and antibiotics [2, 51, 54]. Carefully following the product's safe handling and use instructions is necessary to ensure that the intended pathogens and microbial targets are effectively eliminated. This includes diluting the product according to the label instructions, knowing which surfaces can and should be treated, using the proper application method, limiting or avoiding aerosol products, and if necessary, rinsing treated surfaces with water after application.

Lastly, the effects of prolonged, sublethal QAC exposure on the human skin microbiota are unknown. While the human skin functions as a physical barrier between the external environment and the body proper, it is also colonized by a diverse microbiota that actively influence health and disease [55, 56]. Recent studies have observed that the application of QAC containing cosmetic products can alter the composition and diversity of the skin microbiota and these effects are attributed to the residual activity of the QAC preservatives [55]. Elucidating the effects of chronic QAC exposure on the composition of the human microbiome is an important, yet so far unrecognized, puzzle piece in gaining a holistic understanding of the impact of QAC use on human health.

Conclusions

The production and consumer use of QAC-containing products have risen drastically during the COVID-19 pandemic and are forecasted to continue to increase over the next decade; thus, human exposure to QACs is pervasive and is also expected to further increase. The frequent detection of QACs in blood, tissue and breastmilk indicates that human exposure to QACs is significant and widespread. In a time when cleaning and disinfecting homes and public spaces is a required practice to maintain so-called normalcy, understanding the magnitude and extent of QAC exposure and the associated health effects, and balancing the risk and benefits is paramount. QAC biomonitoring efforts, in conjunction with more extensive toxicological assessments, policy analyses, and public health education campaigns, are recommended to revise best practices for QAC use and limit the potential health risks, particularly for the most vulnerable and at-risk populations.

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Declarations

Conflict of interest Aubrey Frantz declares that they have no conflicts of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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