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Critical Review

Quaternary Ammonium Compounds: A Chemical Class of Emerging Concern

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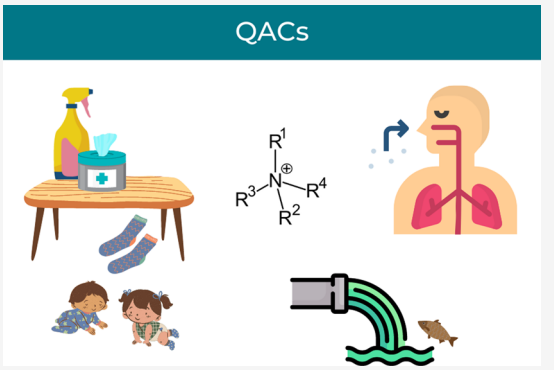
ABSTRACT: Quaternary ammonium compounds (QACs), a large class of chemicals that includes high production volume substances, have been used for decades as antimicrobials, preservatives, and antistatic agents and for other functions in cleaning, disinfecting, personal care products, and durable consumer goods. QAC use has accelerated in response to the COVID-19 pandemic and the banning of 19 antimicrobials from several personal care products by the US Food and Drug Administration in 2016. Studies conducted before and after the onset of the pandemic indicate increased human exposure to QACs. Environmental releases of these chemicals have also increased. Emerging information on adverse environmental and human health impacts of QACs is motivating a reconsideration of the risks and benefits across the life cycle of their production, use, and disposal. This work presents a critical review of the literature and scientific perspective developed by a multidisciplinary, multi-institutional team of authors from academia, governmental, and nonprofit organizations. The review evaluates currently available information on the ecological and human health profile of QACs and identifies multiple areas of potential concern. Adverse ecological effects include acute and chronic toxicity to susceptible aquatic organisms, with concentrations of some QACs approaching levels of concern. Suspected or known adverse health outcomes include dermal and respiratory effects, developmental and reproductive toxicity, disruption of metabolic function such as lipid homeostasis, and impairment of mitochondrial function. QACs' role in antimicrobial resistance has also been demonstrated. In the US regulatory system, how a QAC is managed depends on how it is used, for example in pesticides or personal care products. This can result in the same QACs receiving different degrees of scrutiny depending on the use and the agency regulating it. Further, the US Environmental Protection Agency's current method of grouping QACs based on structure, first proposed in 1988, is insufficient to address the wide range of QAC chemistries, potential toxicities, and exposure scenarios. Consequently, exposures to common mixtures of QACs and from multiple sources remain largely unassessed. Some restrictions on the use of QACs have been implemented in the US and elsewhere, primarily focused on personal care products. Assessing the risks posed by QACs is hampered by their vast structural diversity and a lack of quantitative data on exposure and toxicity for the majority of these compounds. This review identifies important data gaps and provides research and policy recommendations for preserving the utility of QAC chemistries while also seeking to limit adverse environmental and human health effects.



KEYWORDS: *antimicrobial resistance, policy, essential use, regrettable substitution, surfactants, disinfectants, surface coatings, COVID-19, personal care products, softeners, antistatic agents*

INTRODUCTION

Quaternary ammonium compounds (QACs; also referred to as quats) comprise hundreds of chemicals and mixtures. QACs serve many different functions, primarily as antimicrobials, surfactants, preservatives, antistatic and softening agents, and dispersants. They are often found in cleaning products, hand sanitizers, personal care products, many kinds of wipes (surface, baby, hand, and disinfecting wipes), and various

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pesticidal products (Table 1 and Supporting Information Table S1). QACs are frequently incorporated into polymers and used in a variety of applications, including in personal care products (Table S1). QACs are also bonded to surfaces as antimicrobial treatments, including textiles,[1,2] biomedical instruments,[3] and high-touch surfaces in public spaces.[4,5]

Table 1. Common Subclasses of QACs and Associated Products[a]

Subclass	Examples of chemical names (chain length)	Examples of functions and product types
BAC (benzylalkyldimethyl ammonium compounds)	Benzalkonium chloride* Cetalkonium chloride (C16) Alkyl (60%C14, 30%C16, 5%C18, 5%C12) dimethylbenzyl ammonium chloride	-Disinfectant in sprays and wipes -Antibacterial in hand soaps and sanitizers -Preservative in eye drops -Algaecide in swimming pool products
ATMAC (alkyltrimethyl ammonium compounds)	Alkyltrimethyl ammonium chlorides (C20-22) Cetrimonium bromide (C16) Cetrimonium chloride (C16)	-Antistatic/softening agent in hair conditioners and hair care products -Stabilizer and preservative in air fresheners -Corrosion inhibitor in oil and gas operations -Surfactant in hand sanitizers
DADMAC (dialkyldimethyl ammonium compounds)**	Didecyldimethyl ammonium chloride (C10:C10) Dicocoalkyldimethyl ammonium chlorides (C12:C12, C14:C14) Octyldecyldimethyl ammonium chloride (C8:C10)	-Disinfectant in sprays and surface wipes -Antistatic agents in fabric softeners -Biocide in oil field biocidal products -Emulsifier in oil emulsifying products -Corrosion inhibitors in oil and gas operations
EBAC (alkyl dimethyl ethylbenzyl ammonium compounds)	N-alkyl (C12, 68%; C14 32%) dimethyl ethylbenzyl ammonium chloride	-Disinfectant in hand and disinfecting wipes, and all-purpose cleaners -Algaecide in yard and garden applications
APyrC (alkyl pyridinium compounds)	Cetylpyridinium chloride	-Antimicrobial in mouthwashes and toothpastes
Other (e.g., esterquats, polyquaternium compounds)	N,N-bis(2-stearoyloxyethyl)-N,N-dimethylammonium chloride Polixetonium chloride (AKA Polyquaternium 42) Quaternium 15 Benzethonium	-Antistatic agent in fabric softener -Antimicrobial in algaecides and water treatment biocides - Formaldehyde-releasing preservative in cosmetics and personal care products - Antimicrobial in disinfecting cleaners and hand wipes

[a]Structures of some of these subclasses are shown in Figure S1. QAC product types are excerpts from the larger product Table S1. Chemical functions are derived from product ingredient information on manufacturer websites, EPA's CompTox Dashboard,[25] general understanding of QAC uses and applications as described above, and the *Handbook of Applied Surface and Colloid Chemistry*, Vol. 1.[26] Abbreviations by others: *, Benzalkonium chloride as BAC (see further discussion in the text); **, chloride salt of DADMAC C10:C10 as DDAC.

QACs consist of a central ammonium group with a permanent positive charge (see Figure S1) typically bonded to alkyl and aromatic substituents. The boundaries of the class of QACs, and even subclasses of QACs, are not well-defined and encompass an extremely broad array of chemicals. The nature of the bonded substituents and the length of the alkyl chain affect QAC function, performance, environmental fate, and toxicity. QACs used in cleaning and disinfecting products tend to have shorter alkyl chain lengths (C8−C16) than those used in personal care products, which can have alkyl chains as long as 22 carbons.[6] While comprehensive data on the different uses of QACs are lacking, information on approximately 800 QACs used in Canadian commerce was recently made public.[7] Many QACs are high production volume chemicals in the US (>1 million pounds produced or imported annually).[8]

The use of QACs as antimicrobials has increased substantially in response to the COVID-19 pandemic.[9,10] A number of antimicrobial QACs are registered with the US Environmental Protection Agency (EPA) as being effective against common pathogens.[11] QACs are in ∼50% of the products on EPA's List N of disinfectants effective against SARS-CoV-2,[12] which is likely an important driver of the increase in use. QACs are also on EPA's List Q of Disinfectants for Emerging Viral Pathogens.[13,14] Large-scale fogging and spraying of products containing QACs occurs as a COVID-19 control measure, despite the World Health Organization and US Centers for Disease Control and Prevention discouraging these practices as ineffective and potentially harmful.[15,16] Additionally, use of certain QACs has increased in recent years because they are frequent replacements for the 19 active ingredients, including triclosan and triclocarban, banned from use in over-the-counter hand and body washes by the US Food and Drug Administration (FDA) in 2016.[17] While QACs can kill or inactivate a number of different microorganisms in controlled laboratory settings, which is often presumed to be beneficial and marketed to create an impression of cleanliness, evidence of QAC effectiveness in reducing transmission of infectious disease in real world settings and applications, such as the field of healthcare, is limited.[18,19] In addition, no high-quality evidence shows that antimicrobials bonded to surfaces reduce healthcare acquired infections.[20]

Despite widespread use and environmental releases of QACs to the environment, most QACs have not undergone rigorous regulatory assessment for potential adverse human and ecological health effects. In fact, the most basic parameters needed to assess their potential for harm, such as quantitative data on uses and volumes, physicochemical properties, exposure, and toxicity, are lacking for the majority of these compounds. For example, QAC production volume information is difficult to obtain, and environmental releases usually do not have to be reported nor are they routinely monitored in environmental media such as sludge, biosolids, or drinking or surface waters. Also, QACs are not included in the US federal biomonitoring efforts,[21] and the lack of ingredient transparency in many applications makes it difficult to properly characterize the major exposure sources.

The purpose of this review is to summarize what is known about QACs, including environmental properties, occurrence, and ecological effects; human exposure, metabolic fate, and health effects; and antimicrobial resistance. We also briefly describe chemical management strategies in the US. We conclude by identifying the most pressing knowledge gaps and recommending research and policy actions to address these chemicals of emerging concern.

QAC NOMENCLATURE

The nomenclature for QACs is complex and variable. Table 1 shows several subclasses of QACs commonly described in environmental studies, including benzylalkyldimethyl ammonium compounds (BACs), alkyltrimethyl ammonium compounds (ATMACs), and dialkyldimethyl ammonium compounds (DADMACs)[22−24] (Figure S1 depicts the structure of these subclasses). Table 1 also includes alkyldimethyl ethylbenzyl ammonium compounds (EBACs), alkylpyridinium compounds, and other QACs not often included in environmental studies but found in consumer products (see also Table S1).

An example of the inconsistencies in QAC nomenclature is benzalkonium chloride, which has been abbreviated by others as BAC—the definition of BACs in this work (benzylalkyldimethyl ammonium compounds) is broader. The EPA FIFRA program uses slightly different nomenclature for this subclass, calling it alkyl dimethyl benzyl ammonium chloride (ADBAC). Benzalkonium chloride and ADBACs are all mixtures with

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varying alkyl chain lengths, typically ranging from C8 to C18 (C12 to C14 have the highest biocidal activity[5]), but the proportion of each chain length within the mixture varies[12,27] and is often unspecified (see Table S1). While in some instances benzalkonium chlorides may be listed as an inactive ingredient on eye drop packaging, *n*-alkyl (C14, 60%; C16, 30%; C12, 5%; C18, 5%) dimethyl benzyl ammonium chloride may be used to describe the active ingredient listed on a disinfectant package. Further, in environmental studies this may be listed simply as C_{12}- to C_{18}-BACs (i.e., BAC C12−C18). This inconsistent QAC nomenclature leads to confusion and complicates efforts to effectively survey the uses and scientific literature of these compounds. This lack of consistency also makes it difficult for consumers to identify which products contain QACs, even when their use is disclosed.

In this work, we use the abbreviations shown in Table 1 and indicate the number of carbons in the alkyl side chain(s) when known (e.g., BAC C12 or DADMAC C12:C12), or "C-undefined" when unknown. The colon indicates multiple alkyl chain lengths on the same compound (DADMAC C12:C12), while a dash indicates a range of chain lengths (DADMAC C12:C12−C18:C18).

In 1988, the EPA proposed grouping QACs registered for use in pesticidal products into four groups based on chemical structure.[28] These groupings, however, are not widely used in the scientific literature and do not address possible within-group differences (e.g., persistence or toxicity) due to chain lengths nor do they reflect the enormous diversity of structures of QACs. The QACs described in Table 1 predominantly fall into EPA's Group I (alkyl or hydroxyalkyl straight chain QACs) and Group II (nonhalogenated benzyl substituted QACs). Group III refers to di- and trichlorobenzyl substituted QACs, while Group IV encompasses QACs with unusual substituents (charged heterocyclic ammonium compounds). Grouping strategies based solely on structure run the risk of assessing a less harmful QAC and inferring safety for the entire group. Utilizing grouping strategies that consider variables such as alkyl chain length, function (e.g., antimicrobial or not), sensitization potential, common mixtures, and coexposures, and that address the entire class of QACs, would greatly aid in prioritizing immediate actions on the most harmful members of this large and broadly used class of chemicals of emerging concern.

CHEMICAL PROPERTIES AND ENVIRONMENTAL OCCURRENCE

As mentioned previously, QACs have a permanently charged central ammonium ion, although nondissociated salts may exist, including within products and possibly even on surfaces. Compiled experimental and calculated data[29,30] generally indicate high water solubility, low volatility, and low to moderate hydrophobicity (log K_{ow} < 4) for some QACs. Theoretical predictions[30] suggest high hydrophobicity (log K_{ow} > 9) for QACs with multiple aryl or alkyl groups with more than ten carbons, but experimental measurements to confirm these extreme values are currently lacking. Properties of QACs control their fate and occurrence in the multimedia environment: The high water solubility and low hydrophobicity render smaller QACs abundant in wastewater and water; the permanent positive charges facilitate the sorption of QACs to negatively charged solids, especially phyllosilicate clay minerals that are abundant in soil and sediment;[31] and the low volatility limits volatilization loss after indoor applications and contributes to QAC persistence on indoor surfaces.

QAC persistence varies with compound structure and environmental conditions. While QACs are relatively susceptible to aerobic biodegradation and indirect photolysis,[32] the strong affinity of QACs for sorption to particles and solids limits the importance of these processes. Earlier work on other chemicals indicates that sorption to nonaqueous phases remarkably lowers bioavailability of chemicals and thereby suppresses biodegradation.[33] Additionally, reported nonlinear adsorption isotherms indicate that QACs may bind to organic particles more strongly at low concentrations.[34]

Chemical persistence is an important factor in prioritizing chemicals of concern. Current regulatory frameworks often define chemical persistence based on half-lives in surface media (water, soil, sediment, etc.), typically with thresholds on the order of months under conditions that may be idealized for biodegradation (i.e., highly oxygenated, acclimated bacteria, etc.), but these thresholds can vary considerably[35] and may not be reflective of environmental conditions relevant to QACs. Some QACs, particularly those with longer side chains such as DADMAC C18:C18,[23] likely meet regulatory criteria for persistence, depending on the criteria used and studies allowed for consideration. While other QACs may not meet criteria for persistence in water set by existing chemical regulatory frameworks, in some instances they approach the current thresholds.[36] However, QACs' strong affinity for sorption in nonaqueous phases, together with their permanent charges, may reduce the rate of biodegradation, leading to longer than expected half-lives (on the order of years)[23,37] once sorbed to soil and sediment and, thus, meeting the criteria of persistence.[38,39]

In addition, persistence in indoor environments is of particular concern as it increases the potential for exposure, especially for susceptible populations such as children, and because of the role that QACs may play in antimicrobial resistance. Indoors, QACs partition into polar and weakly polar condensed phases, such as carpet, flooring, indoor aerosols, and settled dust. Indoor fate and transport modeling indicates that QACs can substantially partition into the thin layer of organic films on various indoor surfaces and thus be protected from rapid heterogeneous oxidation.[29] Removal of dust and organic films seems to be the main mechanism for the loss of QACs indoors,[29] which often takes days or weeks and thus enables a long presence of QACs indoors. Extended duration of antimicrobials may be a desired feature but can also be problematic for substances of concern due to increased opportunities for exposure. A better understanding of the persistence of QACs in both indoor and ambient environmental settings is needed.

Detection and quantification of QACs is key to assessing their environmental fate. Colorimetric assays have been used for 70 years, and more recent assays use ion association complexes or derivatization, the latter having limits of quantification in the tens of nanomolar.[40−42] While these methods are capable of detecting total QACs, triple quadrupole or high-resolution mass spectrometry is required for the detection and quantification of individual analytes.[37,43−45] The wide variety of chain lengths and hydrophobicity of QACs influence their interaction with the materials (e.g., solid phase extraction cartridges) used for the preconcentration and cleanup of samples. Thus, for a given method, recoveries for different QACs will vary widely. Finding a single method that

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can effectively recover compounds with C2 to C22 chain lengths is an ongoing challenge.

Given the wide variety of QAC uses, there are various pathways from source to the environment (Figure 1).[22] Most

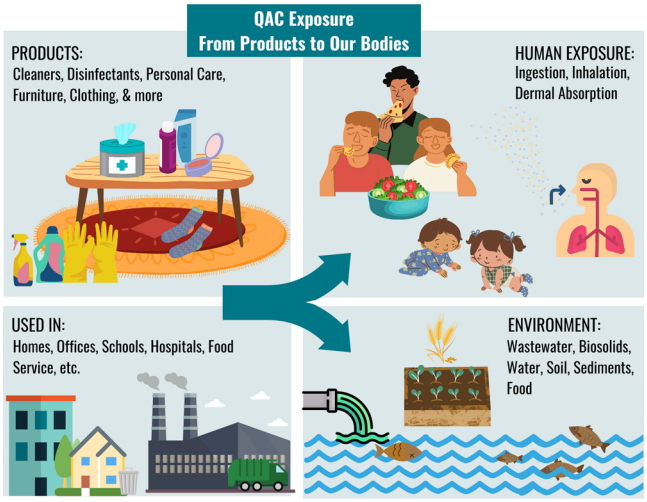

Figure 1. QAC exposure routes from products and other sources, via pathways indoors and outdoors.

usage occurs in indoor environments and leads to QACs entering wastewater treatment plants via the sewage system. Both industrial and residential/commercial discharges are significant sources of QACs in wastewater.[37,46]

QACs persist through wastewater treatment. Levels in wastewater effluent are reported in tens of μg/L,[22,37,47] and are associated with the occurrence of QACs in downstream surface water and sediments. Wastewater influent levels are 10-fold higher, and specific waste streams may have concentrations in the mg/L range.[22,24,37,47−49] While typical levels of QACs in influent are not expected to interfere with treatment processes by inhibiting biological nitrification (the conversion of ammonia to nitrate),[22,48] inhibition could occur sporadically due to concentrated discharge or high usage in specific processes or industries. In aerated biological wastewater treatment systems, QAC removal results from both adsorption to sludge and microbial degradation.[49,50]

Levels in sludge and biosolids as high as 500 mg/kg (dry weight) have been measured.[47,51−53] The presence of QACs in soils could arise from amendment with QAC-containing biosolids, as well as from direct use as surfactants in pesticide/herbicide formulations. QACs have also been detected in soil irrigated with municipal wastewater.[54] The levels and persistence of QACs in soils remain largely unexplored.[24,55] Aerosolized usage of QACs outdoors (e.g., disinfection of outdoor surfaces, agricultural applications) and transport of dust particles are additional pathways by which these compounds could move in the outdoor environment.

Long-term monitoring data are currently insufficient to assess trends in QAC levels in wastewater effluents, biosolids, or sludges. Trends are a function of changes in usage rates and wastewater treatment effectiveness. Recent preliminary results showed an increase of some QAC disinfectants in untreated wastewater[56] and wastewater sludge samples[57] during the early stages of the COVID-19 pandemic.

Wastewater discharges can lead to the presence of QACs in downstream aquatic ecosystems. A recent review of environmental occurrence of QACs (BACs C12−C18, DADMACs C10:C10−C18:C18, ATMACs C12−C18) indicated frequent observations in surface waters from Europe, Asia, and North America, with concentrations of individual compounds generally less than 1 μg/L.[47] Broader data are available for aquatic sediment (BACs C8−C18, DADMACs C8:C10−C18:C18, ATMACs C10−C18);[47] Mohapatra et al. suggested that, for BACs, C12 was generally observed at the greatest abundance, while, for DADMACs and ATMACs, abundance was greater for those compounds with longer alkyl chain length. All water and sediment studies reviewed were conducted before the pandemic. Notably, ATMACs C20 and C22, which are used extensively in hair products, were not reviewed, although they have been shown to be present in sediment at relatively high concentrations.[44]

In aquatic environments, sediment cores can be used to reconstruct long-term temporal trends in QAC contamination, due to the affinity of these compounds for both inorganic and organic particles and their persistence in this matrix. QACs have been examined in sediment cores from lakes in Minnesota,[37] as well as urban estuaries including Jamaica Bay in New York,[23,44] San Francisco Bay in California,[58] the Pearl River Estuary in China, and Tokyo Bay in Japan.[59] Overall, sediment core data indicate the appearance of BACs, DADMACs, and ATMACs in the 1950s, with peak discharges in urban areas typically occurring within the 1960s through 1980s. Declines often follow treatment upgrades at wastewater facilities. Temporal trends specific to individual QACs may reflect changes in use and formulation of consumer products. Examples include greater use of disinfecting and antibacterial products, and reformulation of fabric softeners and hair care products.[23,44]

■ ECOLOGICAL RISKS

Bioavailability of QACs in aquatic ecosystems is modified by their affinity for organic and mineral particles, with studies suggesting that toxicity is primarily driven by exposure to dissolved concentrations.[60,61] Available ecotoxicity data and recent reviews generally indicate QACs may pose risks to biota.[22,24,47,55,62,63] More data are available for biocides, including BACs and shorter chain DADMACs (e.g., C10:C10), due to regulatory requirements. Toxicity varies with algal species and QAC structure,[55] with BACs and DADMACs generally considered highly toxic to freshwater and estuarine/marine algae. Fifty percent effective concentrations (EC50s) are as low as 14 μg/L for BAC C12−C16[64] and 11 μg/L for DADMAC C10:C10,[65] and lowest and no observed concentrations (LOECs/NOECs) are as low as 1 μg/L for BACs and DADMACs.[55]

For aquatic invertebrates, *Daphnia magna* (*D. magna*) is particularly sensitive, with lowest reported acute EC50s for BAC C12−C16 and DADMAC C10:C10 of 5.8 μg/L[64] and 18 μg/L,[65] respectively. LOECs and NOECs as low as 0.006 μg/L have been reported for aquatic invertebrates subjected to chronic exposures to BACs.[55] However, chronic toxicity thresholds for *D. magna* are generally similar to acute toxicity thresholds, suggesting a nonspecific mode of action.[66,67] Although QACs are persistent in aquatic sediment, chronic toxicity data for larval *Chironomus tentans*, a freshwater midge, indicate relatively low sediment toxicity (adverse effects expected at >100 mg/kg dry weight for BAC C12−C16 and DADMAC C10:C10).[66,67]

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Studies of fish indicate many QACs are moderately to highly toxic, depending on species and end point. A review of acute toxicity data in freshwater fish species reveals 50% lethal concentrations (LC50s) as low as 64 μg/L for BACs and 1 μg/L for DADMACs,[55] and sublethal effects can occur at exposures below LC50s.[68] For regulatory purposes, however, higher LC50s of 280 μg/L (fathead minnow, *Pimephales promelas*) and 190 μg/L (zebra fish, *Brachydanio rerio*) are used for BAC C12−C16 and DADMAC C10:C10, respectively.[65−67,69] Chronic toxicity tests indicate NOECs of 32 μg/L for both of these QACs.[65−67,69] Very few studies are available for estuarine or marine species.[62,65−67,69]

QAC concentrations in aquatic ecosystems are approaching protective toxicity thresholds, such as predicted no effect concentrations (PNECs) calculated using single-species studies like those described above. European regulatory assessments for biocidal applications of BACs (C12−C16) and DADMACs (C10:C10) list PNECs of 0.415 and 1.1 μg/L, respectively.[66,67] Reported monitoring data, thoroughly compiled in a recent review, indicate surface water concentrations exceed the PNEC for BACs in some locations, but not for DADMACs.[24,47,68] For ATMACs, the European Chemicals Agency (ECHA) lists a range of freshwater and marine PNECs depending on chain length. For example, ATMAC C16 has freshwater and marine PNECs of 0.42 μg/L and 0.042 μg/L, respectively;[66,67] limited available freshwater monitoring data suggest concentrations do not exceed freshwater thresholds.[47,70]

Preliminary evidence suggests QAC mixtures are likely to have additive aquatic toxicity, though synergistic or antagonistic behavior has been observed for some QAC combinations. Hora et al. calculated a simplified, general PNEC for QACs of 0.10 μg/L using the geometric mean of all available *D. magna* acute toxicity EC50 values for BACs, DADMACs, and ATMACs and a protective assessment factor of 1000.[22] Comparison of this PNEC to average reported surface water concentrations of ∼0.07 μg/L for single QAC compounds and ∼0.28 μg/L for summed QACs suggests potential risks associated with current and future concentrations. To inform robust risk evaluation for aquatic ecosystems, key data gaps to address include chronic toxicity data, studies of mixture toxicity, and comprehensive exposure measurements, especially for wastewater effluent dominated systems. Specific data gaps have been noted for EBACs, APyrCs, and benzethonium chloride.[22,37]

Data on QAC exposure and toxicity to terrestrial organisms are even more limited.[24] Repeated applications of wastewater-derived biosolids or QAC-containing agricultural products may result in QAC accumulation in soils; however, limited bioavailability reduces overall risk to biota.[22,68]

HUMAN EXPOSURE

Exposure Routes. Humans can be exposed to QACs via several routes including dermal, hand-to-mouth, inhalation/ingestion of contaminated dust, and inhalation of aerosolized QACs (Figure 1). Acute high-level exposure is typically accidental. For example, exposure to QAC concentrates can cause dermal corrosion and burns[71−73] and children and dementia patients have experienced sometimes fatal oral exposure.[74] The primary focus of this review is chronic exposure resulting from the manufacture and use of QAC-containing products. For example, if not wiped off after disinfection, QACs can stay on surfaces, which would lead to postapplication exposure. In the latter case, exposure routes include touching disinfected hard surfaces, unintended hand-to-mouth contact (e.g., ingestion of both surface residues and dust-bound QACs),[75] and dermal absorption of chemicals present on hands after surface-to-hand contact. Li et al.[29] modeled human exposure to 14 QACs after their application to indoor hard surfaces. Assuming the applied disinfectants are not wiped off after disinfection, hand-to-mouth contact was found to contribute most (>90%) to postapplication exposure. For shorter chain QACs (e.g., BAC C8), dermal absorption also matters but is not the primary exposure route (contributes less than 10% of postapplication exposure).[29] Based on their affinity for materials like cotton and rayon,[76] significant residues of QACs are likely to remain on textile surfaces long after application.[77,78]

Some QACs easily adsorb to airborne particles and dust. Zheng et al.[45] measured 19 QACs (BACs, DADMACs, and ATMACs) in residential dust collected before and during the COVID-19 pandemic. QACs were detected in >90% of the samples collected during the pandemic at concentrations ranging from 1.95 to 531 μg/g (median 58.9 μg/g). The total QAC concentrations in these samples were significantly higher than in samples collected before the pandemic (median 36.3 μg/g) and strongly correlated with disinfection frequency in homes. Similarity in the profiles of QACs in dust and disinfecting products used in these homes suggested that these products are an important source of QACs in house dust.

Lebouf et al.[79] reported high concentrations of some QACs (including BAC C12−C16, benzethonium chloride up to 5.31 μg/m^3) in the air shortly after spraying a QAC-containing product. Zheng et al.[80] found that background QAC concentrations (including several BACs, DADMACs, and ATMACs) in residential indoor air (with no direct spraying in the sampled area) can reach up to 4.36 μg/m^3. ATMACs (common in personal care products, including air fresheners; Table S1) were the most abundant QACs in the latter samples, contributing 78% to the total QAC concentrations. The abundance of ATMACs in air can be explained by their relatively lower octanol−air partition coefficients (log K_{OA} 8.17−11.8), compared to BACs and DADMACs (log K_{OA} 11.0−18.2). These findings suggest that inhalation could be important for more volatile QACs. Food and water are other possible sources of exposure as QACs are used widely for sanitation in food production, processing, and services; and they can be found in surface water.[81,82]

Highly Exposed Populations. Workers who manufacture cleaning products and those in occupations that use QAC-containing cleaning and disinfection products, such as housekeeping, domestic cleaning, facilities maintenance, health care, hospitality, food services, and food production and processing, are more highly exposed than the general population. Medical equipment preparers, housekeepers, floor strippers/waxers, endoscopy technicians, nurses, and dental assistants report commonly spending over an hour per shift using QAC-containing products.[83] Women are more highly exposed to cleaning and disinfecting products both at home and work.[84−86]

Teachers, students, childcare providers, and children in daycares may also have elevated exposures, as industrial cleaners and sanitizers are commonly used in these settings.[87] School staff and their students used disinfectants extensively during the COVID-19 pandemic, in some cases unsafely and without instruction on proper handling and use.[88] Sanitizers and disinfectants are also commonly used in correctional

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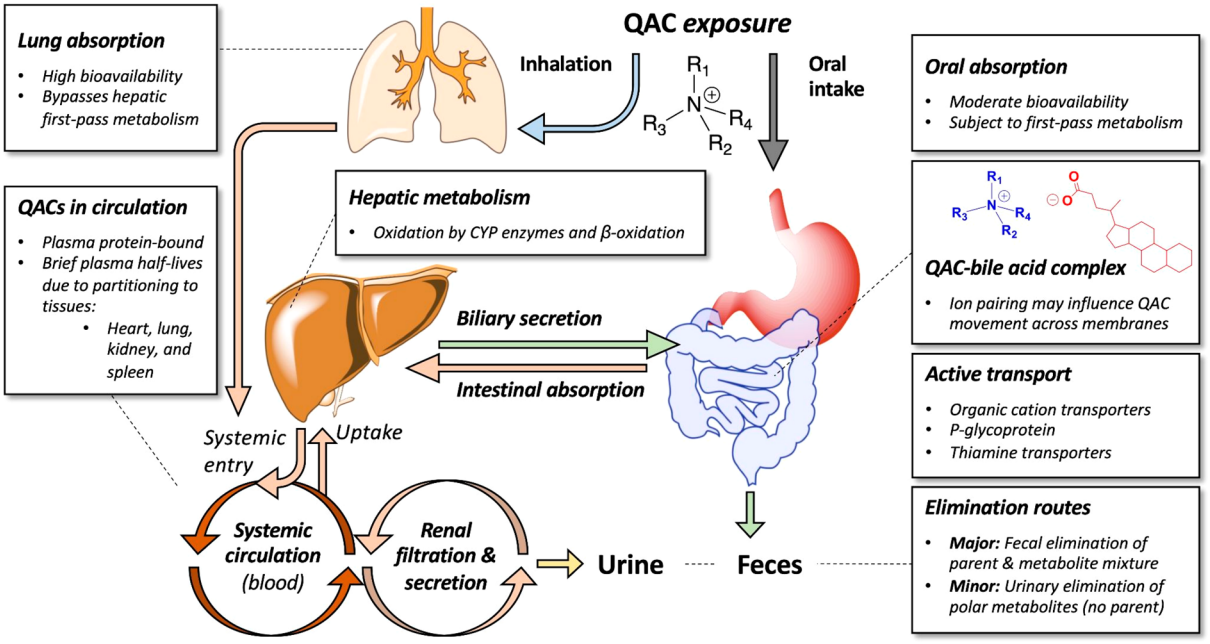

Figure 2. Proposed ADME routes for QACs based on in vitro and in vivo data on some subgroups of QACs in humans and animals.

facilities and detention centers. Troubling exposures in these settings were reported during the pandemic.[89,90]

Among the general population, children may experience greater exposure to QACs than adults. Li et al.[29] modeled the daily uptake of 14 QACs (ATMAC C16, BACs C8−C18, EBACs C12−C14, DADMACs C8:C8−C10:C10, benzethonium chloride) by children (aged 3), teenagers (aged 14), and adults (aged 25) resulting from indoor hard surface disinfection. The results indicate that children have 14−55 times higher daily uptake of these QACs compared to teenagers and adults due to their more frequent hand-to-mouth contact.

Biomonitoring Data. Exposure to QACs is not currently monitored by the National Health and Nutrition Examination Survey (NHANES).[21] In 2021, QACs were added to the California Environmental Contaminant Biomonitoring Program's list of priority chemicals, but to date no data have been collected.[84−86,91]

What we know about human exposure to QACs is mostly from academic studies. QACs have been detected in blood from the general population, with higher levels observed during the pandemic. Hrubec et al.[92] measured five QACs (BACs C10−C16, DADMAC C10:C10) in human plasma collected prior to the COVID-19 pandemic and reported up to 80% detection frequency with total QAC concentrations ranging from 0.01 to 58.7 ng/mL (median 1.9 ng/mL). Zheng et al.[80] analyzed human serum from 222 Indiana residents collected before and during the COVID-19 pandemic. Fifteen QACs (ATMACs C12−C18, BACs C8−C18, DADMACs C8:C8−C10:C10 and C14:C14−C18:C18) were detected in up to 97% of the samples. The total QAC concentrations in samples collected during the pandemic were significantly higher than those measured in blood collected before the pandemic (medians 6.04 ng/mL vs 3.41 ng/mL, a 77% increase). ATMACs were the most abundant QAC group in both sample groups and contributed 50−66% of the QAC concentrations. The prevalence of ATMACs in blood is similar to that in indoor air, suggesting that inhalation could be an exposure pathway leading to buildup in blood. In addition, oxidative metabolites of BACs were detected in human urine[93] and were consistent with published work on BAC metabolism by human hepatic cytochrome P450.[94]

QACs have also been found in breast milk, suggesting that breastfeeding could be an important exposure pathway for nursing infants. Zheng et al.[95] identified 13 QACs (ATMACs C8−C18, BACs C10−C18, and DADMACs C8:C8−C10:C10) in breast milk collected from women in the US. The median total QAC concentration in breast milk was 1.5 ng/mL, and the most abundant QACs included BACs C12−C16 and ATMACs C14−C18.

Metabolic Fate. Absorption, distribution, metabolism, and excretion (ADME) of QACs in humans is poorly understood. However, based on the available data in human and animal studies, we have summarized the proposed ADME routes in Figure 2.

Absorption. Several acute incidents of high-level exposure indicate that QACs are readily detectable in human blood following oral ingestion.[96−102] In one case of oral BAC poisoning,[102] BACs C12, C14, and C16 were still present in blood (115, 123, and 16 ng/mL, respectively) when the individual died 18 days postingestion, but these BACs were undetectable in urine. Another case involving substantially higher oral BAC exposures and levels in blood also found that parent BACs were undetectable in urine.[100] These cases of acute exposure suggest that QACs may be orally absorbed and persist in humans, and indicate that renal secretion is poor.

A dermal penetration study funded by QAC manufacturers Lonza and Henkel detected only trace amounts of BACs (low- to sub-nM) in plasma after extensive hand washing with 0.13% BAC antiseptic wash.[103] Thus, an intact skin layer appears to be an effective barrier to dermal uptake of certain QACs under hand washing conditions.

While cases of QAC ingestion in humans have demonstrated oral bioavailability, the absorption mechanisms and specific bioavailability values of QACs have not been studied in humans. In rats, Kim et al.[104] observed that oral bioavailability

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of a model QAC compound (tributylmethyl ammonium) increased with dose from 17% up to 35%. The dose-dependent bioavailability is attributed to saturation of intestinal P-glycoprotein (P-gp) efflux at higher doses.[104,105] Furthermore, P-gp gene knockout mice displayed enhanced persistence of intravenously (IV)-dosed QACs.[106] In rats dosed orally with cetyltrimethylammonium (ATMAC C16) or BACs (C12 and C14),[107,108] time courses show intestinal absorption occurs over several hours, with these QACs persisting beyond 24 h in blood and tissues. Rats that aspirated BAC material into their lungs experienced efficient and rapid absorption as evidenced by several-fold higher levels of BACs in blood and tissues relative to rats dosed orally. These animal studies establish moderate oral bioavailability of QACs, with inhalation leading to greater exposure, which is likely due to efficient absorption in the lung and the bypassing of the first-pass metabolism in the liver.

Transport and Excretion. Studies performed mainly on model QAC compounds (typically tetraalkyl ammonium compounds) suggest that several transporters, including P-glycoprotein (P-gp), organic cation transporters (OCTs), and thiamine transporters (ThTRs), may contribute to QAC disposition in the human body. While QACs were found to be poor P-gp substrates, the ion pair complexes between model tetraalkyl QACs and bile acids are efficiently transported by P-gp.[109,110] P-gp at the bile canalicular membrane of hepatocytes may facilitate hepatobiliary QAC excretion. Additionally, various QACs are excellent substrates of OCTs.[110−112] Involvement of OCT transport in the disposition of QACs may explain the hepatobiliary excretion (OCT1), renal accumulation (OCT2), and accumulation in the heart (OCT1/3) in animals as discussed below. ThTRs transport dietary vitamin B1 (thiamine), which also contains a quaternary nitrogen. Benzethonium and ATMAC C16 were recently shown to interact with ThTR-2,[113] the transporter primarily involved in intestinal absorption and renal proximal tubular reabsorption of thiamine. Further study is needed to determine the role of these transporters in QAC disposition with the highest priority given to the QACs with emerging human exposure data (ATMACs, BACs, DADMACs, etc.), and eventually extending broadly to the wide range of QACs of toxicological interest.

QACs in circulation may bind plasma proteins, such as albumin and α-1-acid glycoprotein;[80,114−116] however, plasma half-lives of BACs C12, C14, and C16, dosed via IV bolus to rats, are somewhat brief (1.8−3.7 h) and volumes of distribution are high (5.6−6.7 L/kg), suggesting that partitioning into tissues is favored over retention in plasma. IV-administered BACs accumulated in heart, lung, spleen, and kidney, which was consistent with earlier findings by Xue et al.[101,108] No parent BACs were detected in urine, confirming urine is not a preferred excretory pathway for the parent BACs. Additional studies are needed on the tissue distribution and excretion routes of other QACs.

IV administration of QACs to bile-cannulated rats established that higher molecular weight (MW) QACs (>200) are preferentially excreted from the liver into bile.[117,118] Commercial disinfecting QACs generally have MW values >300, so it can be reasonably assumed that QACs in the body are mostly excreted into bile regardless of the administration routes. Rats given a single IV dose of ^{14}C-radiolabeled BACs excreted 45−55% of radioactivity to feces (likely through bile) and 20−30% to urine (possibly as metabolites), with 30−35% remaining in tissues/carcass at 7 days postadministration.[119−121]

Metabolism. Seguin et al. reported metabolism of BACs C10, C12, C14, and C16 by human cytochrome P450s (CYPs), the main xenobiotic metabolizing enzymes.[94] CYP2D6 and several CYP4F isoforms produced the major oxidative metabolites of BACs. Significantly, a series of oxidized BAC metabolites were found in human urine samples, further confirming human exposure to QACs and their metabolism by CYPs (unpublished data).[91] Expanded identification and incorporation of polar human QAC metabolites excreted into urine and feces in biomonitoring studies will allow for an enhanced understanding of human QAC exposures.

A study conducted in rats by Luz et al. found that oral dosing of ^{14}C-radiolabeled BACs (C12, C14, and C16) or DADMAC (C10:C10) resulted in 88−98% recovery of radioactivity in feces, wherein substantial fractions (1/3 for BACs or 1/2 for DADMAC) presented as oxidized metabolites.[119−121] While Luz et al.[119] proposed that *". . .microbes in the intestinal tract are likely responsible for metabolism. . ."*, oxidation reactions are not typically associated with xenobiotic metabolism by gut microbiota,[122] likely because the luminal space of the intestine is hypoxic. Conversely, recent evidence confirming the metabolism of BACs C10−C16 by CYPs[94] suggests that lipophilic QACs are likely susceptible to oxidation by CYPs. Furthermore, oxidized BAC metabolites were observed in the brain, liver, and blood of mice fed a BAC-containing diet, indicating intestinal absorption.[123] However, intestinal metabolism and absorption may vary among species and should be further elucidated. As both parent QACs and metabolites can be excreted via biliary and intestinal transport, fecal samples would be suitable for biomonitoring of QACs and QAC metabolites.

Bioaccumulation. Zheng et al.,[80] determined the bioaccumulation potentials of 18 QACs (ATMACs, BACs, and DADMACs) with alkyl chain lengths of C8−C18 in an in vitro−in vivo extrapolation model using the results of human hepatic metabolism and serum protein binding experiments. The in vitro clearance rates determined for these QACs decreased with increased length of the alkyl chain, similarly to the findings reported by Seguin et al.[94] Generally, ATMACs were metabolized at slower rates than BACs and DADMACs. Bioaccumulation of QACs was further confirmed through the analysis of blood (sera) samples (n = 222). The QACs with slower predicted in vivo clearance rates were detected at higher levels in serum. The lowest predictions of in vivo clearance rates (0.114−0.505 mL/h/g liver, respectively) were determined for ATMACs C12−C16, and these compounds were found at relatively high concentrations in analyzed blood samples.

HEALTH EFFECTS

Studies in which specific end points and health effects are identified are shown in Table S2.

Dermal, Respiratory, and Immune Effects. The immune system plays a central role in mediating many dermal and respiratory effects observed following QAC exposures. Hypersensitivity is an excessive immune response to allergens that also can be accompanied by chronic inflammation. Skin irritation can involve both inflammatory and hypersensitivity responses. These underlying immunological responses of hypersensitivity, irritation, and inflammation, may be common

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mechanisms driving dermal, respiratory, and other types of immune-specific and immune-related effects of QACs described below.

Dermal Effects. Skin irritation, sensitization, and dermatitis associated with QAC exposure have been reported in some human studies. Various studies have found that exposure to quaternium 15, a formaldehyde-releasing preservative used in personal care products, is linked with allergic contact dermatitis.[124−126] A study in patients with suspected allergic contact dermatitis found 5.5% with positive skin sensitization reactions to the chloride salt of BAC C-undefined, but infrequent reactions to quaternium 15.[127] A review of patients tested for allergic contact dermatitis concluded that the chloride salt of BAC C-undefined is a skin irritant and sensitizer.[128] A study of patients with suspected contact sensitization to occupationally used disinfectants concluded that clinically relevant sensitization to the chloride salt of DADMAC C10:C10 is rare.[129]

Cases of allergic contact dermatitis linked with some QAC exposures have been reported, including the chloride salt of APyrC C16 in latex gloves;[130] quaternium 15 in a lotion,[131] hair products,[132] and electroencephalography skin preparation gel;[133] and *N*,*N*-didecyl-*N*-methylpoly(oxyethyl) ammonium propionate in a dental clinic disinfectant.[134] Robinson et al.[135] described cases of a rare skin condition in children who were exposed to the chloride salt of BAC C-undefined via clothing washed with an antibacterial laundry rinse aid.

In animal studies, the National Institute for Occupational Safety and Health found that mice dermally exposed to the chloride and bromide salts of DADMAC C10:C10 displayed both skin irritation and allergic sensitization.[136,137] The researchers identified an immune basis for the response observed in mice exposed to the chloride salt of DADMAC C10:C10.[138] Immune response gene expression was altered in the skin tissue of mice exposed to the chloride salts of DADMAC C10:C10 or BAC C-undefined.[139]

ECHA and EPA risk assessments of the chloride salts of BACs C12−C16[66,69] and the chloride salt of DADMAC C10:C10[65,67] have not classified these compounds as skin sensitizers.[119] Further research is needed on exposure potential and dermal effects of other QACs that are in personal care products (e.g., polyquaternium compounds, the chloride salt of ATMAC C22) and therefore likely or intended to contact the skin.

Respiratory Effects. Exposure to some QACs is associated with work-related asthma and other possible respiratory effects. The Association of Occupational and Environmental Clinics has identified the chloride salts of some BACs and DADMAC C10:C10 as sensitizer-induced asthmagens, or substances known to cause asthma newly acquired from a workplace exposure.[140] Studies conducted among hospital staff,[141] staff in other sectors,[142] and case reports[143−146] have found exposure to QAC-containing disinfectants and cleaning products to be linked to work-related asthma. Bellier et al.[147] described a study in which subjects were exposed via inhalation to a QAC diluted in water. Of four QACs tested, subjects reacted most frequently to the chloride salt of DADMAC C10:C10. These authors suggested that QACs may induce work-related asthma through a specific immunological response-sensitizing mechanism and that irritation could also play a role. There are challenges in characterizing human exposure to QAC-containing products (e.g., data gaps in quantitative exposure measurements, use of multiple types of QAC-containing products), and in mechanistically linking these exposures with asthma.[148,149]

In a prospective cohort study of female nurses in the US, high-level exposures to disinfectants and cleaning products, including QAC-containing items, were significantly associated with increased risk of chronic obstructive pulmonary disease, independent of asthma and smoking status.[86]

Respiratory effects have also been reported in animal studies. Mice exposed to aerosols of various QACs (the chloride salt of BAC C-undefined, the bromide salt of ATMAC C16, the bromide salt of DADMAC C18:C18, and the chloride salt of APyrC C16) had reduced lung tidal volume and increased respiratory rate. The exposures to the chloride salts of BAC C-undefined and APyrC C16 also gave rise to pulmonary inflammation.[150] Studies of rats exposed to the aerosolized chloride salt of BAC C-undefined have reported effects such as pulmonary cell damage and inflammation,[151] and nasal cavity and lung irritation.[152] Increased markers of pulmonary inflammation were observed in mice exposed to the chloride salt of DADMAC C10:C10 via intra-tracheal instillation.[153]

ECHA reported that although no experimental data were available, the chloride salts of BACs C12−C16 and the chloride salt of DADMAC C10:C10 are not expected to be respiratory sensitizers.[66,67,119]

More information on the specific QACs used in disinfecting sprays and foggers, perfumes, and air fresheners would help determine which QACs should be evaluated for their ability to be inhaled. Biomonitoring data from individuals who regularly use these sprayed products would aid in quantifying the extent of work-related exposures. Inhalation toxicology studies of respirable QACs are essential for understanding their potential respiratory and pulmonary effects.

Immune Effects. A pilot study examining the immune response to QAC exposure in humans reported that 80% of participants had blood residues of BACs C12−C16 and DADMAC C10:C10 and a dose-dependent increase in inflammatory cytokine concentrations.[92] While the clinical significance of this increased inflammation remains to be determined, blood of some individuals from this study had QACs at levels associated with adverse effects in experimental animal studies.

Abdelhamid et al.[154] evaluated ambient exposure to BACs C12−C16 and DADMAC C10:C10 in a mouse model of autoimmunity. Using MRL/lpr mice, models of Systemic Lupus Erythematosus were used to evaluate several immune end points, including markers of innate and adaptive immunity. The authors found that rather than exacerbating autoimmune markers, QAC exposure in this model attenuated signs of autoimmunity. Other measured markers, however, indicated that neutrophils, cells of innate immunity, may have hindered expansion of autoreactive T cells and/or exacerbated T cell apoptosis. Neutrophils in this model possessed a phenotype often seen in patients who experience sepsis, and combined with other findings, led Abdelhamid et al.[154] to conclude that in this model, QAC exposure was immunosuppressive.

Immune effects of QAC exposure so far are primarily limited to descriptive observational measures. Studies assessing functional outcomes such as antigen-specific antibody responses, cell-mediated cytotoxicity, or host resistance would help delineate effects of QACs on a challenged immune system.

Reproduction and Development. *Reproductive Effects.* Reproductive toxicity in mice was accidentally discovered

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when unexpected infertility was traced back to use of a vivarium cleaning product. A 6 month breeding trial in mice exposed orally to a commercial cleaning product containing BACs C12−C16 and DADMAC C10:C10 demonstrated infertility and decreased fecundity.[155] Follow-up studies identified similar effects in mice orally dosed with a mixture of purified BACs C12−C16 and DADMAC C10:C10 formulated similarly to the commercial product, or with ambient exposure to the commercial product used in the mouse room.[156] Adverse outcomes were dose-dependent and included longer time to first litter, increased pregnancy interval, and fewer total litters.[155] Reproductive effects were identified for both males and females.[156] Female outcomes included increased time between estrus cycles, reduced ovulation and implantation, and increased postimplantation losses. Male outcomes included decreased sperm concentration and motility.[156] A different study using CD rats failed to find reproductive effects,[157] but the rat study did not assess a mixture similar to the commercial cleaning product, only the BAC (C12−C16) and DADMAC (C10:C10) separately. The rat study also did not assess sperm concentration and mobility or estrous/ovulation.

The potential for reproductive toxicity of QACs is highlighted in a patent from 1975 titled "Method for the Control of Fertility"[158] that presents studies demonstrating that dietary administration of QACs to dogs and rats is embryocidal, ovicidal, and/or spermicidal. The patent included any QAC salt with a structure of a central positively charged nitrogen with four substituents and a variety of anions. Notably, BACs are an active spermicidal ingredient in some sponges, vaginal creams, and capsules currently sold in some countries;[159] BAC and APyrC C16 bind to the estrogen receptor to exert antiestrogenic effects.[160] No human epidemiologic studies on reproduction or development were identified in our review.

Developmental Effects. Exposure to a commercial cleaning product containing BACs C12−C16 and DADMAC C10:C10 impaired embryo development, caused neural tube defects (NTDs), and increased embryonic death in mice.[161] Effects were similar for pregnant mice exposed ambiently to the commercial cleaning product containing BACs C12−C16 and DADMAC C10:C10 used to clean the vivarium, or a mixture of purified BACs C12−C16 and DADMAC C10:C10 formulated similarly to the commercial product. NTDs were observed regardless of the timing of exposure (continuous, prebreeding period, or the window of embryo vulnerability for neural tube closure) and regardless of whether it was the male or female parent that was exposed. Up to 20% of embryos in a litter were affected, a 1000-fold increase over the background rate for the mouse strain. Multiple defects were occasionally seen in an individual embryo at different neural tube closure sites. NTDs are not typically lethal but exposure increased both early embryo death (resorptions) and late term fetal deaths, suggesting the mixture may affect more than the developing nervous system. Effects on the placenta may play a role, as the placental size was generally not proportional to the size of the fetus (e.g., large fetuses with small placentas and small fetuses with large placentas—conditions that can affect fetal viability).

Another study reported limited developmental toxicity with reductions in pup body weights at the highest dose but no effect on litter size.[157] The study used CD rats as opposed to mice and fed either BAC (C12−C16) or DADMAC (C10:C10) rather than as a mixture similar to the commercial cleaning product. The study did not evaluate other end points such as NTD formation or placental development. Hrubec et al. found the occurrence of NTDs in rat embryos to be considerably lower than in mice,[161] indicating that rats may be more resistant to developmental toxicity. Replicating the Hrubec et al. study in rats would help elucidate whether rats are indeed more resistant.

Biochemical Effects. *Cholesterol and Lipid Homeostasis.* Cholesterol plays important roles in embryonic and neural development.[162−164] Alterations in cholesterol biosynthesis lead to various developmental disorders.[165] In 2016, Herron et al. found that BACs significantly inhibit cholesterol biosynthesis at low nM concentrations in neuroblastoma cells.[166] Specifically, shorter chain BACs, such as BAC C10 and C12, potently inhibit 3b-hydroxysterol-Δ7-reductase (DHCR7), the last step of the cholesterol biosynthetic pathway, while longer chain BACs (C14 and C16) likely inhibit an earlier unidentified step. The same activities were also observed in a 3D culture of neural progenitor cells.[167] However, in an in vivo study on neonatal mice born to dams fed a BAC-containing diet, inhibition of DHCR7 was not observed in the neonatal brains,[123] likely due to the low concentrations (around 1 nM) of BACs observed in the neonatal tissues. In contrast, an overall decreased level of total sterols was observed in either BAC C12 or BAC C16 (BAC C14 not tested in this study) exposed mouse brains, suggesting an inhibition of cholesterol biosynthesis at a step before the formation of the first sterol, lanosterol. Furthermore, upregulation of cholesterol biosynthesis genes was observed, which was consistent with the inhibition of cholesterol biosynthesis by individual BACs. In the same study, the authors found that diglycerides, triglycerides, ceramides, and hexosylceramides were also significantly affected by BACs. In another study by the same group,[94] ω- and (ω − 1)-hydroxylated metabolites of BAC C10 displayed greatly reduced potency in inhibiting DHCR7, suggesting CYP metabolism is potentially detoxifying.

In a study by Hrubec et al. examining the correlation between QAC levels in human blood and several biological measurements, some sterols were significantly correlated with certain QAC levels.[92] In particular, DADMAC C10:C10 was highly correlated with lanosterol, zymosterol, desmosterol, and 8-dehydrocholesterol. Although the sample size is small, the strong preliminary data justify a large-scale human study to examine relationships between QAC exposure and toxicological end points.

Mitochondrial Bioenergetics. Mitochondria are the major source of energy in the form of ATP in animals including humans. Apart from energy generation, mitochondria perform many biochemical reactions critical for cellular and tissue homeostasis. Along with the better understanding of the role of mitochondria in physiological and pathological states,[168] recent decades have seen a sharp rise in reports recognizing pharmaceuticals,[169] and environmental pollutants such as QACs[160,170] as previously unidentified mitochondrial toxicants.

Chemically, most QACs can be classified as lipophilic cations that can accumulate into a negatively charged mitochondrial matrix. Evidence of direct inhibition of mitochondrial oxidative phosphorylation comes from multiple in vitro studies involving several QACs (BACs C10−C18, APyrC C16, and tetraoctyl ammonium).[160,171,172] Inácio et al.[173] evaluated several types of QACs (ATMAC C10, APyrC C12, and BAC C12) individually and demonstrated that, at

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lower concentrations, QACs (ATMAC C10) inhibit mitochondrial oxidative phosphorylation at complex I in vitro which precedes their surfactant action and concluded from the study that inhibition of mitochondrial oxidative phosphorylation by QACs is the most likely mechanism underlying the antimicrobial effects of QACs. No study, however, has explicitly related mitochondrial inhibition to antimicrobial activity. Additionally, chain length can play an important role in mitochondrial toxicity of QACs. When tested in mitochondrial toxicity assay, BAC C8 did not show any mitochondrial inhibition, whereas BAC C12, C14, and C16 were all mitochondrially toxic. The individual BACs (C12, C14, and C16), however, were less potent inhibitors of mitochondrial oxidative phosphorylation in vitro compared to the mixture (unpublished data). Consistent with these studies, a pyridinium-based gemini QAC (two pyridinium-based QACs in one compound) inhibited respiration in a yeast model at an approximately 2.5-fold lower concentration than the concentrations causing membrane damage.[174,175] Notably, in an acute time frame, QAC-based disinfectants predominantly show surfactant aka membrane dissolving effects on bacteria due to their high concentrations of QACs. The long-term antibacterial effects of these products may be due to their mitochondrial inhibitory property at lower concentrations, which has not been completely studied yet. In another study, Inácio et al.[176] demonstrated that there is a differential sensitivity to APyrC C12 between bacteria and mammalian cells with bacteria being more sensitive. This differential sensitivity suggests that there could be a "therapeutic window" for the QACs; i.e., there is a possibility to safely use the QACs for general disinfection purposes without adversely affecting mammalian cells. However, the practical application of this differential sensitivity needs to be explored in the context of persistence in the environment and chronic reexposure, which may lead to increased antimicrobial resistance.

Research indicates that APyrC C16,[160] and ATMAC C10[173] inhibit mitochondrial respiration in vitro. Datta et al.[160] observed antiestrogenic activity of APyrC C16 in vitro and hypothesized that it is mediated through effects on mitochondrial function. ATMAC C10 induced the generation of intracellular reactive oxygen species, particularly superoxide anion[173] which is consistent with impairment of the mitochondrial respiratory chain. The consequences of mitochondrial inhibition by QACs in both microbes and mammalian cells need further elucidation to determine the role it plays in the antimicrobial effects and other deleterious effects in the mammalian system.

Predictive Toxicology. In vitro and predictive toxicology studies can be important data sources for QACs that have little or no publicly available health effect information. These methodologies likely will be relied upon more heavily by regulatory bodies like the EPA to reduce and replace vertebrate animal testing.[177] The EPA's Chemistry Dashboard[25] contains some QAC bioactivity data from ToxCast/Tox21 assays.[178] Of approximately 100 unique QAC CASRNs searched, 29 had ToxCast/Tox21 bioactivity information; 21 of these QACs were active in at least 100 assays. Some examples of the diversity of QAC bioactivities reported at subcytotoxic concentrations include ATMAC C12 effects on G protein-coupled receptor binding and altered cell proliferation, ATMAC C18 impacts on altered gene expression, and DADMAC C16:C16 effects on CYP expression, enzyme activity, and cell morphology. The use of new approach methodologies such as quantitative structure−activity relationships and ToxCast/Tox21 testing may be helpful for grouping and prioritization of the most harmful QACs. However, assessing the utility of these methods with regard to QACs is beyond the scope of this review.

Antimicrobial Resistance. Antimicrobial chemicals, including disinfectants and antibiotic drugs, have an important role in preventing and curing infections, but their efficacy is jeopardized by the evolution of antimicrobial resistance. Indeed, there were nearly 5 million deaths associated with antimicrobial resistance in 2019.[179] In addition to human and veterinary medicine, an increasing body of evidence points to the use of disinfectants and cleaning products as a contributor to antimicrobial resistance.[47,180,181] For example, tolerance to BAC was described in the Gram-negative opportunistic pathogen *Serratia marcescens* as early as the 1950s.,[46,181,182]

At concentrations lethal to microorganisms, QACs are purported to either dissolve cell membranes or inactivate cytoplasmic enzymes.[47,183] At sublethal concentrations, however, conditions favor the survival of some microorganisms over others, particularly those with resistance.

Certain microorganisms can form coatings, e.g., spores, which effectively protect against QACs.[184] Resistance conferred by features of the outermost layer of the cell (i.e., spore coat, cell wall, or outer membrane) is termed "intrinsic".[185] Accordingly, disinfectant tolerance is generally highest in spores, followed by Gram-negative bacteria and finally Gram-positive bacteria. This pattern holds true for QACs. For example, surfaces embedded with BAC C12−C16 are relatively ineffective against spores,[186] and hospital surfaces cleaned with an unspecified QAC were enriched for Gram-negatives compared to surfaces cleaned with bleach.[187]

In addition to intrinsic resistance, microorganisms can acquire resistance through mutation and horizontal gene transfer. Acquired resistance develops in response to exposure, particularly at sublethal concentrations, and spreads with increasing application.[182] as shown in various organisms via a variety of mechanisms.[47,181,188]

Members of the genus *Pseudomonas* are of particular interest when it comes to antimicrobial resistance, as they are widespread in the environment and include one of the most nefarious drug-resistant pathogens: *Pseudomonas aeruginosa* (*P. aeruginosa*). One reason *P. aeruginosa* is so difficult to treat is its rich arsenal of efflux pumps, which can extrude multiple antimicrobials, including QACs, as well as antibiotic drugs.[189] Tolerance of QACs, and particularly BACs, has been repeatedly observed.[190,191] In *Pseudomonas*, tolerance has been attributed to lipid production or changes in membrane lipid composition,[183] increase in phospholipids and fatty and neutral lipids,[191,192] modification of cell surface charge, and efflux.[193] In *P. aeruginosa*, BACs C-undefined induced aggregation,[192] which has important implications for population-level behaviors, e.g., biofilm formation. While BACs are equally as effective against *P. aeruginosa* in planktonic and biofilm forms,[194] biofilm formation may limit the efficacy of other disinfecting strategies if not preceded by cleaning to remove the biofilm. In some cases, increased tolerance to BACs was associated with a change in resistance to other QAC C12−C14 or C-undefined,[195,196] disinfectants, or clinically relevant antibiotics.[196]

The presence of other organisms in the environment may enhance survival in the face of disinfectant stress. In dual-species biofilms, the presence of *Lysteria monocytogenes* (*L.*

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monocytogene) provided a protective effect for *Pseudomonas putida* (*P. putida*) from treatment with sublethal concentrations of BAC C-undefined, which preferentially killed the *L. monocytogenes*.[197] Also, the presence of *Pseudomonas fluorescens* enhanced resistance[198] to a mixture of QACs (BACs C-undefined, DADMACs C8:C8−C10:C10) in *Salmonella enterica* in dual-species biofilms.[199] *Salmonella* species are particularly relevant for food production, where QACs are also often used as disinfectants; however, nearly three-quarters of *Salmonella* isolated from swine slaughterhouses were resistant to unspecified QACs.[200] In multispecies biofilms, sublethal concentrations of BACs C-undefined select for *Pseudomonas* and *Bacillus* species.[201] Thus, tolerance is not only a function of the intrinsic properties of the organism or the presence of acquired traits but also the presence of other microorganisms in the environment.

Despite being widespread in the environment, studies of the impact of QACs on antimicrobial resistance in situ are rare. However, a recent study demonstrated that exposure of soil microbial communities to BAC C12 increased both the absolute and relative abundance of several antimicrobial resistance genes.[202] Critically, this enrichment was most pronounced at 1 and 10 mg/kg. This concentration range is directly relevant to BAC concentrations observed in sediment (0.008 to 5.325 mg/kg; C12−C18) and sludge (14.568 mg/kg; C10−C16).[46]

Finally, above and beyond resistance, microorganisms may also gain the ability to use an antimicrobial as a source of nutrients or energy. Indeed, organisms closely related to *Pseudomonas nitroreducens* and *P. putida* are implicated in assimilatory BAC degradation.[203] This phenomenon not only benefits the degrading organisms but may also confer protection to others in the community due to the bystander effect.

Whether through intrinsic or acquired mechanisms, or due to indirect effects of other microorganisms, antimicrobial resistance is a critical problem. A substantial body of evidence points to QACs as exacerbating this problem, notably in drug-resistant pathogens of concern, e.g., *P. aeruginosa*.[47] Following the COVID-19 pandemic, an increase in antibiotic resistance was observed.[204] This phenomenon was likely caused by a confluence of factors, of which the increased use of QAC-based disinfectants may be one. Exposure of bacteria to disinfectants is expected to result in an increase in resistance, both to QACs and clinically relevant antibiotics.[205] Problems associated with tolerance range from disinfection failure, to cross-resistance to medically relevant antibiotic drugs (e.g., through multidrug efflux).[46,189]

QAC Management in the U.S. The degree of US governmental oversight of QACs depends on how a specific compound is used. The EPA regulates QAC-containing products marketed with pesticidal claims under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Chemical risk assessments under FIFRA use a structure-based grouping approach in which a selected model compound is assessed (e.g., for the BAC group, the model compound is BAC C12−C16, CAS Reg. No. 68424-85-124, and for the DADMAC group, DADMAC C10:C10, CAS Reg. No. 7173-51-5 is used).[199] Inferences are then made from these model compounds to the larger group. One problem with this approach is that basing groups solely on structure runs the risk of assessing a less harmful QAC and inferring safety for the entire group. Studies described above indicate differences in toxicity between QACs that are structurally similar but differ by a few carbons. Examples of other variables that could be used to group QACs are alkyl chain length, function (e.g., antimicrobial or not), sensitization potential, common mixtures, and coexposures. These variables may be more useful in identifying the most hazardous QACs with the highest exposure potential. The FIFRA grouping approach also applies only to pesticides and does not address the many frequently used QACs with possible bioactive properties and high potential for exposure and environmental release.

EPA has also addressed some QACs through their Safer Choice Program, specifically the Safer Chemical Ingredient List (SCIL) that identifies products with ingredients deemed safer for human health and the environment. SCIL lists several QACs as ingredients of the lowest concern within the functional class of surfactants.[205] Unfortunately, while the SCIL criteria are publicly available,[206] the chemical-specific health and environmental hazard information is not, making it difficult to determine the degree to which these QACs have been assessed, particularly for hazard end points identified in this review.

EPA's Toxic Substances Control Act (TSCA) governs chemicals in products not regulated by other agencies or programs (generally everything except food additives, drugs, cosmetics, and pesticides). This includes many QACs used in products listed in Table S1. Chemicals regulated under TSCA are subject to less rigorous risk assessment requirements than those managed under FIFRA.[206,207] Access to information about QACs also varies depending on how the QAC is used. While manufacturers who make pesticidal claims need to have their labeling information (i.e., active ingredient concentrations, consumer warnings, information about how to obtain directions on proper use) reviewed and approved by the EPA under FIFRA, many of the products listed in Table S1 (e.g., hair conditioners, fabric softeners) that utilize the same QACs for other purposes or without making pesticidal claims can be sold without providing the same type of information to the end user. Additionally, QAC uses in many applications (e.g., surface coatings and durable products) usually do not have to be disclosed—this makes it difficult to identify which products contain QACs. A more consistent approach to availability of information and the rigor of assessment for the entire class of QACs is warranted.

Chemicals used in pharmaceuticals, cosmetics, or food additives are regulated by their respective FDA programs. As noted above, QACs were frequent replacement chemicals in over-the-counter hand and body washes after the 2016 FDA ban of 19 active ingredients, including triclosan and triclocarban, for these uses.[17] The ban was based on a lack of additional benefit compared with non-antibacterial soap and water, and insufficient evidence of their safety. The original version of the FDA rule also included benzalkonium chloride and benzethonium chloride, but they were removed from the final rule to allow manufacturers more time to submit data on their safety and effectiveness. The FDA has granted several extensions to submit data, which have been publicly reported through 2020,[208] but has yet to make a ruling on these two QACs. A 2018 study concluded that benzalkonium chloride and benzethonium chloride are more toxic than triclosan and triclocarban to the environmental model organisms nematodes and zebrafish and that they should not be considered safer alternatives in this respect.[209] Given the seven year delay and the growing evidence of adverse environmental and human

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health impacts, including QACs role in antimicrobial resistance, if FDA lacks evidence of added benefit, they should proceed to finalizing their ruling as soon as possible.

Both the EPA and FDA use hazard and risk data to estimate risks associated with chemicals within their jurisdictions. Regulatory risk assessments are typically limited to data from guideline studies conducted by the regulated community. Such studies have been criticized for assessing end points that are not sensitive enough to detect many adverse health outcomes associated with chemical exposure.[210] Relevant academic studies described throughout this work, including those demonstrating adverse effects at ambient levels of QAC exposure, and exposure assessments predicting risks to children are not systematically incorporated into decision making.[29]

In recent years, a number of jurisdictions in the US and the EU have taken actions regarding QACs. For example, BACs are no longer approved for use in consumer hand and body washes in the EU.[211] Quaternium 15 is banned from cosmetics in the EU[212] and will be banned from cosmetics and personal care products manufactured or sold in California beginning in 2025.[213] Also, in 2021, QACs were added to the California Environmental Contaminant Biomonitoring Program's list of priority chemicals.[214] In 2021, the Massachusetts Toxics Use Reduction Institute Science Advisory Board recommended listing BACs and DADMACs as toxic or hazardous substances. If adopted, this listing will require annual use reporting and reduction planning by businesses.[215] These recent actions signal growing concern about the use and potential for exposure to certain QACs and whether human and ecological health are sufficiently protected under current policies and regulations.

The fact that there is already widespread exposure and growing evidence of adverse environmental and human health impacts of QACs suggests that source control to reduce exposure should be considered, for example, through the essential-use approach.[206] The essential-use approach states that chemicals of concern should only be used where their function is necessary for health and safety, or is critical for the functioning of society, and no safer alternatives exist. This approach has been used in various contexts beginning with the 1987 Montreal Protocol to phase out certain ozone-depleting substances (e.g., chlorofluorocarbons).[216] It is also currently being applied to per- and polyfluoroalkyl substances in European REACH regulations.[217] Examples of potential non-essential uses of QACs include odor and static prevention, some surfactant and emulsifier uses, and antimicrobial treatments in furniture.[218,219] Where their use might be essential, such as for disinfection, safer alternatives can often be identified.[220] For example the Design for the Environment program, which helps purchasers find antimicrobial products that meet both the EPA antimicrobial registration requirements and safer ingredient standards, lists the following safer alternatives for certain uses: hydrogen peroxide, citric acid, ethanol, and lactic acid.[221] Eliminating QAC uses that are not required for health and safety or where safer alternatives exist could quickly reduce human exposure as well as releases to the environment.

Recommendations. QAC use is increasing, without high-quality evidence of their effectiveness in reducing transmission of infectious disease in many settings and applications.[18] Meanwhile, greater indoor usage is consistent with higher indoor exposure, which is a concern given the recent discovery of adverse health outcomes in laboratory animals at relatively low (ambient) exposure concentrations. Increased production and usage is anticipated to result in higher QAC concentrations in wastewater, which is a pathway for broader environmental exposure and potential risks to biota. This is especially concerning given that some environmental concentrations already exceed protective aquatic toxicity thresholds. Furthermore, excessive use of QACs likely contributes to the global problem of antimicrobial resistance.

This review supports the need for a comprehensive research and policy agenda to expand our understanding of QACs while simultaneously taking action to protect human and ecological health. Toward this end, we make the following recommendations:

General Research Recommendations.

- Research a broader suite of QACs, beyond the relatively few currently studied compounds, including QACs not registered as antimicrobials.
- Continue to develop and improve analytical methods for QACs in different sample matrices (e.g., dust, air, water, sediment/soil, blood, urine, feces, breast milk).
- Conduct studies on common mixtures of QACs, including in environmental media, humans, wildlife, or products, and their possible health effects, to establish protective concentrations and environmental thresholds.

Environmental Research Recommendations.

- Conduct comprehensive monitoring of wastewater influent, effluent and biosolids, as well as impacted surface waters, to better understand the fate and transport of QACs in the environment and potential sources and exposure pathways for biota.
- Perform experimental and theoretical research on the physicochemical properties, environmental and biological behavior, and fate and transport of a wide array of QACs. In particular the persistence of QACs in soil/sediment needs to be better understood.

Human Health Research Recommendations.

- Conduct quantitative exposure surveys and collect comprehensive biomonitoring data on QACs and QAC metabolites in blood, urine, and feces (e.g., in the general public through NHANES and in highly exposed populations via National Institute for Occupational Safety and Health (NIOSH) or the Nurses' Health Study.[222] The State of California may be ideally positioned to convene such a study given that QACs are on Biomonitoring California's list of priority chemicals.
- Study QACs in indoor environments to better characterize human exposure (dermal, inhalation, and ingestion) directly from products and through routes such as household air and dust. In particular, better understanding of the indoor persistence of QACs of varying chain lengths is needed.
- Conduct additional research on metabolic fate to better understand how QACs are absorbed, distributed, metabolized and excreted by the human body and how these differ from model species such as rats and mice.
- Carry out human epidemiological and animal toxicity studies of respiratory, immune, reproductive, developmental, and other sensitive end points to replicate and expand on current findings in animal models.

Policy Recommendations.

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- Include QACs on lists of contaminants of emerging concern used for reporting, monitoring, assessment, etc. This should also include QACs not registered as antimicrobials but used in large quantities or detected in the environment (see Table S1).
- Regulate QACs consistently across different uses and agencies and consider exposure from multiple sources when evaluating allowable concentrations, formulations, and conditions of use.
- Require full disclosure of the exact QACs used in all products, their functions (including for non-antimicrobial use such as material preservation or odor control), and production volumes. Achieving full transparency from manufacturers will likely require legislative or regulatory changes and collaboration across all relevant government agencies.
- Develop a generally agreed upon definition of the entire class of QACs, perhaps with the help of the National Academies of Science and Medicine, to better understand the scope of the problem and support research and policy initiatives. This should include establishment of naming conventions that specify alkyl chain length, possible subgroups, and identification of QACs likely to have antimicrobial activity.
- Reevaluate the 1988 EPA grouping strategies to better characterize and prioritize QACs for further research and management. An effort should be made to include all QACs, not just substances regulated under FIFRA. In addition to structure, other potentially relevant methods to group QACs should also be considered, such as alkyl chain length, function (e.g., antimicrobial or not), sensitization potential, common mixtures, and coexposures. New approach methodologies such as quantitative structure−activity relationships and ToxCast/Tox21 may be helpful in this effort.
- Revisit QACs on the EPA Safer Chemical Ingredient List to ensure that they have been assessed for end points of concern identified for other QACs. As part of this process, health and environmental hazard data used for such assessments should be publicly available.
- Finalize the FDA assessments regarding safety and effectiveness of benzalkonium chloride and benzethonium chloride in over-the-counter hand and body washes.
- Establish a more rigorous process to incorporate academic findings in investigations of health or environmental hazards of QACs carried out by regulatory agencies. This research should be used to direct the regulated community to expand their research to include sensitive end points, QACs of varying chain lengths, and suspected adverse health effects of commonly used mixtures (e.g., BACs and DADMACs).
- Immediately address the known threat of antimicrobial resistance. The medical field recommends that antibiotics be prescribed only when necessary and educates the public about proper use. Similar efforts to eliminate non-essential uses of antimicrobial QACs in consumer products are warranted. An example would be product labeling requirements such as "To reduce the public health threat of antimicrobial resistance, use this product only when disinfection is necessary and not for general cleaning". Manufacturers should also be discouraged from implying a health benefit of QAC use in coatings and other durable product treatments without supporting evidence that these treatments are effective in reducing the transmission of infectious diseases.

QACs are a very large and diverse class of chemicals. Until we better understand possible differences among subgroups, it would be prudent to assume that all QACs could pose some level of risk. This is justified given the known impacts of antimicrobial resistance, biomonitoring data indicating their presence in humans, and recent data on adverse health outcomes. To effectively manage risks in a timely manner, the entire class of QACs should be addressed. For example, identifying and removing unnecessary uses of QACs, pointing to existing safer alternatives for essential uses, and incentivizing innovation of safer alternatives can prevent harm. We believe the research presented in this review supports such actions to preserve human and ecological health.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.2c08244.

(Table S2) Adverse health effects associated with specific QACs in humans and rodent models; (Figure S1) example structures and associated acronyms for some of the most well-studied subclasses of QACs (PDF)

Table S1 showing examples of QACs used in a variety of formulated consumer products (XLSX)

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Notes

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