Potential Designated Chemicals:
Quaternary Ammonium Compounds

Materials for March 4, 2020 Meeting of the Scientific Guidance Panel
for Biomonitoring California[1]

Introduction

At the July 2019 meeting of the Scientific Guidance Panel (SGP), the Office of Environmental Health Hazard Assessment (OEHHA) presented a preliminary screen of quaternary ammonium compounds (QACs) for possible future consideration as designated chemicals for Biomonitoring California (OEHHA, 2019). The SGP recommended that OEHHA prepare a potential designated chemical document on QACs.

This summary provides a brief overview of information relevant to the criteria for designated chemicals, which address the following areas[2]:

- Exposure or potential exposure to the public or specific subgroups
- Known or suspected health effects
- Analytical considerations
- Need to assess the efficacy of public health actions to reduce exposure to a chemical

This is not a comprehensive review of the full body of literature on QACs. Highlights of findings from selected published studies are included; secondary sources are also cited. A complete list of references consulted is provided on pages 19-30.

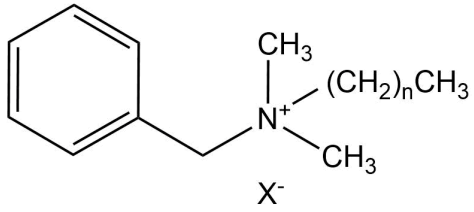
If the Panel were to recommend adding QACs as a class to the list of designated chemicals, any member of the class could be considered for measurement in future Biomonitoring California studies.

[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.
[2] For the complete list of criteria refer to Health and Safety Code section 105449; these criteria are not joined by the term “and.”

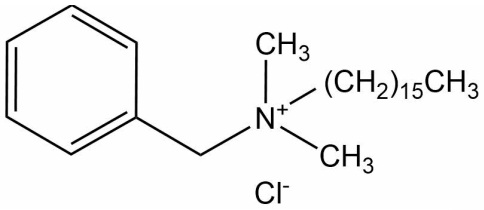
Chemical identity

The class of QACs (also referred to as “quats”) is diverse and includes hundreds of chemicals and chemical mixtures. QAC structures generally include NR_4^+, where R is often an alkyl or benzyl group. Within this class, there are sub-classes that have different chemical properties. Some of these include benzylalkyldimethyl ammonium, dialkyldimethyl ammonium, and alkyltrimethyl ammonium compounds (BACs, DADMACs, and ATMACs, respectively):

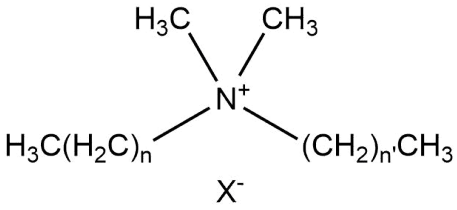
General BAC structure



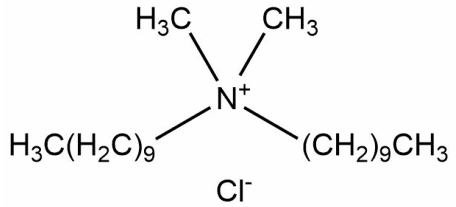
Example BAC:
Benzylhexadecyldimethyl ammonium chloride



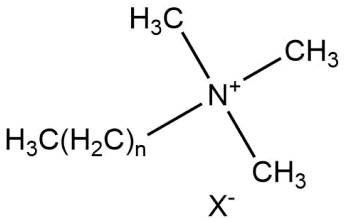
General DADMAC structure



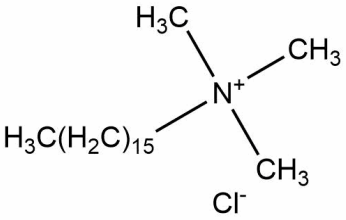
Example DADMAC:
Didecyldimethyl ammonium chloride



General ATMAC structure

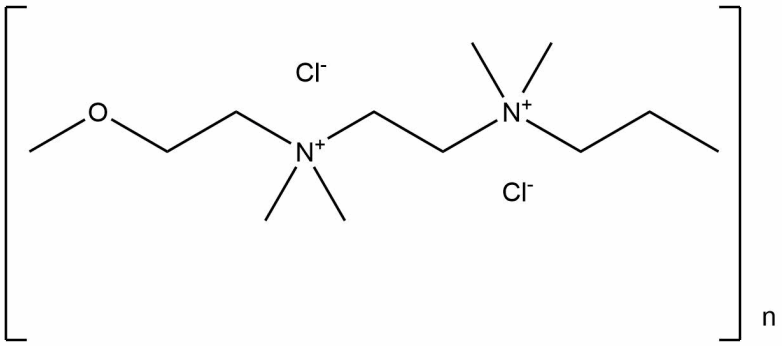


Example ATMAC:
Hexadecyltrimethyl ammonium chloride

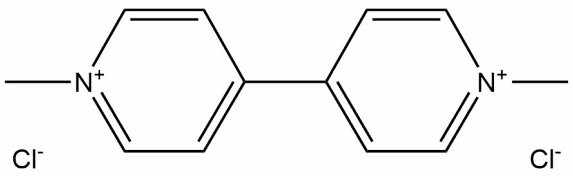


Other examples include polyquaternium compounds, quaternary ammonium (QA) herbicides, and esterquats:

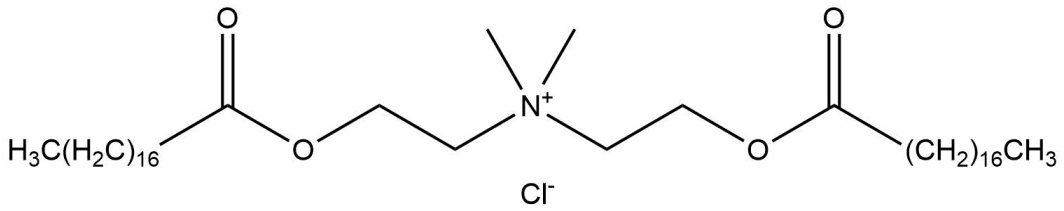
Structures of other example QACs



Example polyquaternium compound:
Polixetonium chloride



Example QA herbicide:
Paraquat dichloride



Example esterquat:
N,N-Bis(2-stearoyloxyethyl)-N,N-dimethylammonium chloride (Esterquat 1)

Exposure potential

QACs have a wide range of uses, including as antimicrobials, disinfectants, preservatives, surfactants, antistatic agents, softeners, conditioners, herbicides, and corrosion inhibitors. A number of QACs and QAC mixtures are high production volume chemicals (i.e., over 1 million pounds per year). Harrison et al. (2020) noted that benzalkonium chloride[3] is being used widely as a replacement for triclosan in hand soaps marketed as antimicrobial. Some QACs registered as pesticides are sold in California at greater than 1 million pounds per year. Refer to OEHHA (2019) for more details on the types and volume of use.

LeBouf et al. (2017) developed a method to detect some QACs in air and surface wipe samples from a US hospital. A 15-minute area air sample was collected while a housekeeper actively cleaned a hospital bathroom with a spray containing less than 1% benzalkonium chloride (60% C14, 30% C16, 5% C12) by weight. The measured air

[3] Benzalkonium chloride can also be referred to as alkyldimethylbenzyl ammonium chloride. These compounds are BACs, as defined on page 2 above, and have varying alkyl chain lengths. We provide alkyl chain length information in this document if it is specified by the authors of the cited references.

concentrations in this sample were 1.5 micrograms per cubic meter (μg/m^3) benzyltetradecyldimethyl ammonium chloride (14 carbon [C] chain length), 0.96 μg/m^3 benzylhexadecyldimethyl ammonium chloride (C16), and 0.23 μg/m^3 benzyldodecyldimethyl ammonium chloride (C12), which were comparable proportions to that in the spray. Another 15-minute area air sample taken while a housekeeper swept a hospital waiting room, but not while any QAC-containing disinfectants were being used, contained 1.2 μg/m^3 benzyltetradecyldimethyl ammonium chloride, 0.15 μg/m^3 benzylhexadecyldimethyl ammonium chloride, 3.5 μg/m^3 benzyldodecyldimethyl ammonium chloride, and 0.46 μg/m^3 benzethonium chloride. The authors remarked that these findings demonstrated that their method "was capable of collecting quats in the air over short periods from nonspraying sources." Eight-hour area air samples from locations where QAC-containing cleaning and disinfecting products were generally used contained 0.028 μg/m^3 benzyltetradecyldimethyl ammonium chloride, 0.006 μg/m^3 benzylhexadecyldimethyl ammonium chloride, and 0.011 μg/m^3 benzyldodecyldimethyl ammonium chloride. Surface samples of a nurse's station contained 23.8-76.6 micrograms per 100 square centimeters (μg/100 cm^2) benzyltetradecyldimethyl ammonium chloride, 10.5-28.8 μg/100 cm^2 benzylhexadecyldimethyl ammonium chloride, and 6.9-21.8 μg/100 cm^2 benzyldodecyldimethyl ammonium chloride.

A study of indoor house dust samples (n = 50) collected as part of the 2003-2006 German Environmental Survey for Children detected averages of 30.2 milligrams per kilogram (mg/kg) benzalkonium chlorides (primarily benzyldodecyldimethyl ammonium chloride and benzyltetradecyldimethyl ammonium chloride) and 5.0 mg/kg didecyldimethyl ammonium chloride (analytical "limits of determination" for each QAC: 0.1 mg/kg; Friedle et al., 2008).

EFSA (2013) analyzed various food samples (n = 5,472) for residues of didecyldimethyl ammonium chloride and benzalkonium chloride compounds of alkyl chain lengths from C8 to C18. Most of the samples (n = 5,168) analyzed did not contain quantifiable levels of these QACs. However, in the category of "milk and milk products," 90 of 239 samples with quantified results had positive detections of at least one of the QACs measured (limit of quantification [LOQ]: 0.01 mg/kg). The highest mean value for didecyldimethyl ammonium chloride was 3.64 mg/kg in milk and milk products. The highest mean value for the sum of benzalkonium chloride compounds with C10 to C16 chain lengths was 14.4 mg/kg in unprocessed grapefruit (LOQ: 0.005 mg/kg).

In an evaluation of benzalkonium chloride residues in various food samples, the German Federal Institute for Risk Assessment (BfR) detected the highest levels in milk (n = 17/38 samples > LOQ; median: 0.15 mg/kg; maximum: 6.66 mg/kg), cream (n = 32/35 samples > LOQ; median: 0.31 mg/kg; maximum: 6.76 mg/kg), and ice cream (n = 49/122 samples > LOQ; median: 0.22 mg/kg; maximum: 21.67 mg/kg). Lower residue levels were detected in foods of plant origin, such as citrus fruit

(n = 14/105 samples > LOQ; median: 0.035 mg/kg; maximum: 0.11 mg/kg) and fresh herbs (n = 22/310 samples > LOQ; median: 0.092 mg/kg; maximum: 0.61 mg/kg) (BfR, 2012).

Kaj et al. (2014) detected various BACs, DADMACs, and ATMACs in fish, mostly cod and some perch, caught from various Nordic lake and marine areas. These QACs were detected in most fish muscle samples, and the summed concentration range was 1-43 nanograms per gram (ng/g), mostly dominated by ATMACs. For example, hexadecyltrimethyl ammonium chloride was detected in 53% of fish muscle samples tested (n = 19 samples; median: 4.7 ng/g; min: < 2.4 ng/g; max: 13 ng/g), and docosyltrimethyl ammonium chloride was detected in 16% of samples tested (n = 19 samples; median: < 1.8 ng/g; min: < 1.4 ng/g; max: 30 ng/g). The three fish liver samples analyzed were all collected from the Oslo fjord, an area that receives effluents from a large wastewater treatment plant (WWTP), and had a summed QAC concentration range of 290-5,800 ng/g. This sum was dominated by docosyltrimethyl ammonium chloride, which was detected in 100% of the samples (n = 3 samples; median: 460 ng/g; min: 250 ng/g; max: 5,400 ng/g).

A sample obtained from a swimming pool treated with a benzalkonium chloride-containing algaecide contained 0.013 milligrams per milliliter (mg/mL) benzyldodecyldimethyl ammonium chloride and 0.0031 mg/mL benzyltetradecyldimethyl ammonium chloride. These concentrations are about 1000-fold lower than in the concentrated algaecide, which contained 19.17 mg/mL and 2.16 mg/mL of each of these QACs, respectively (Ford et al., 2002).

QACs have been widely detected in sewage sludge and sediments. Table 1 (adapted from Zhang et al., 2015) summarizes selected detections in US urban estuarine sediments. Zhang et al. (2015) also summarized detections of a variety of QACs in surface waters across the globe. A study by the US Geological Survey measured benzalkonium chloride in surface water samples collected downstream from WWTPs in two states (Kansas and Missouri) (Ferrer and Furlong, 2001); levels ranged from 1.2 to 36.6 micrograms per liter (µg/L). Pati and Arnold (2020) measured QACs in wastewater effluent and lake sediment samples collected in Minnesota (Minneapolis-Saint Paul metropolitan area). They reported average concentrations in the wastewater samples ranging from 0.4 µg/L to 6.6 µg/L for the total combined target and suspect QACs, which included various BACs and DADMACs.

Table 1. Selected detections of QACs in US urban estuarine sediments (adapted from Zhang et al., 2015)

Location	BACs	DADMACs			ATMACs	Total QACs	Reference
		C8:C10	C10:C10	DTDMACs[1]			
	All values reported in mg/kg (units converted from Zhang et al. [2015] in some cases)						
Forge River, New York (NY)	0.121-21	--	--	1.7-52	--	1.8-74	Li and Brownawell (2009)
Jamaica Bay, NY	--	--	--	--	0.481-2.82 (1998) 1.6-6.75 (2008)	1.6-6.75 (2008)	Lara-Martín et al. (2010)
NY/New Jersey Harbor and Jamaica Bay, NY	0.1-17.7 (median: 1.4)	ND[2]-0.767 (median: 0.01)	ND-4.1 (median: 0.19)	0.69-110 (median: 26)	0.0086-5.3 (median: 0.52)	0.98-114 (median: 29)	Li and Brownawell (2010)

1. Ditallowdimethyl ammonium compounds (DTDMACs) are DADMACs that primarily contain chain lengths of C16:C16, C16:C18, or C18:C18. These longer chain compounds are used in personal care products (e.g., hair care items), for their anti-static and surfactant properties, and were historically used in fabric softeners (Kaj et al., 2014; US EPA Chemistry Dashboard; Weston et al., 2003).
2. ND: Non-detect.

Known or suspected health effects

Associations between human exposures to QACs and the potential for adverse health outcomes, such as skin irritation and respiratory effects, have been examined in a number of studies. Laboratory studies have evaluated various QACs for additional effects, including reproductive outcomes, effects on the immune system, and altered cellular function. Selected studies reporting known or suspected health effects linked with exposure to QACs are described here.

Dermal effects

The US Environmental Protection Agency (US EPA) summarized guideline toxicology studies for "alkyl dimethyl benzyl ammonium chloride"[4] (US EPA, 2017a) and didecyldimethyl ammonium chloride (US EPA, 2017b). These studies reported that alkyldimethylbenzyl ammonium chloride was a dermal irritant, but not a dermal or photo sensitizer in acute toxicity studies. Skin irritation was also observed in subchronic studies of rats and guinea pigs exposed to alkyldimethylbenzyl ammonium chloride (US EPA, 2017a). Didecyldimethyl ammonium chloride was corrosive in acute dermal irritation studies in rabbits, but was not a skin sensitizer in acute studies in guinea pigs. Skin irritation was observed in subchronic studies of rats and guinea pigs exposed to didecyldimethyl ammonium chloride (US EPA, 2017b). The European Chemicals Agency (ECHA) has summarized guideline toxicology studies for "alkyl (C12-16) dimethylbenzyl ammonium chloride"[5] (ECHA, 2015a) and didecyldimethyl ammonium chloride (ECHA, 2015b), both of which have registered biocide uses as wood preservatives. ECHA (2015a; 2015b) reported that both of these compounds were corrosive in acute studies, and can be regarded as skin irritants, but not sensitizers.

The National Institute for Occupational Safety and Health (NIOSH) found that mice dermally exposed to didecyldimethyl ammonium chloride displayed both skin irritation and allergic sensitization (Anderson et al., 2016).

Quaternium 15 was one of the most frequent allergens in a hand contact dermatitis study using data from the North American Contact Dermatitis Group (Warshaw et al., 2007). In comparison, benzalkonium chloride was one of the less frequently found allergens in this same study. Perrenoud et al. (1994) reviewed the frequency of sensitization to preservatives in Swiss patients who had suspected allergic contact dermatitis. The percentage of positive skin sensitization reactions to benzalkonium

[4] US EPA (2017a) used alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride as the model compound, providing a CASRN (Chemical Abstracts Service Registry Number) of 68424-85-1. This compound is referred to with the simplified name of "alkyldimethylbenzyl ammonium chloride" hereafter.

[5] ECHA (2015a) evaluated alkyl (C12-16) dimethylbenzyl ammonium chloride, using the same CASRN cited by US EPA (2017a) of 68424-85-1. ECHA (2015a) reported ranges for the percentages of each chain length: C12 (39-76%), C14 (20-52%), C16 (< 12%). This compound is referred to with the simplified name of "alkyldimethylbenzyl ammonium chloride" hereafter.

chloride was 5.5%, one of the highest reported. For quaternium 15, the percentage was 1.0%, which was among the lowest reported.

Cases of allergic contact dermatitis linked with some QAC exposures have been reported, including cetylpyridinium chloride in latex gloves (Steinkjer, 1998); quaternium 15 in a moisturizing lotion (Cahill and Nixon, 2005), rinse-off hair products (Tosti et al., 1990), and electroencephalography skin preparation gel (Finch et al., 2001); and N,N-didecyl-N-methylpoly(oxyethyl) ammonium propionate in a dental clinic disinfectant (De Quintana Sancho et al., 2014). Quaternium 15 is a formaldehyde-releasing preservative used in cosmetics and other personal care products; allergic contact dermatitis is linked with exposure to quaternium 15, as well as to formaldehyde alone (de Groot et al., 2010; Fasth et al., 2018).

Respiratory effects

Studies conducted among hospital staff (Gonzalez et al., 2014) and staff in other health and social sectors (Paris et al., 2012), and case reports (Bernstein et al., 1994; Burge and Richardson, 1994; Purohit et al., 2000) have found exposure to QAC-containing disinfectants and cleaning products to be linked with work-related asthma. Other potential triggers were examined, such as occupational use of chlorine/bleach and latex gloves (Gonzalez et al., 2014), and use of hairdressing products and non-QAC-containing cleaning products (Paris et al., 2012), and found to not be linked with work-related asthma. A retrospective case series analysis concluded that a substantial proportion of participants who experienced asthma symptoms related to cleaning materials suffered from sensitizer-induced occupational asthma, predominantly caused by QACs (Vandenplas et al., 2013). Bellier et al. (2015) described a study in which patients were challenged with a QAC in water. The authors listed the compounds tested as didecyldimethyl ammonium chloride, alkyldimethylbenzyl ammonium chloride[6], didecyldimethyl ammonium propionate, or benzalkonium chloride.[6] The most frequent QAC to induce a positive inhalation challenge was didecyldimethyl ammonium chloride. 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.

LaKind and Goodman (2019) reviewed human studies of asthmagenicity and occupational cleaning. They evaluated case reports linking occupational exposure to QACs with asthma and concluded that, “Taken together, these case reports, particularly those that provided detailed information on specific inhalation challenge testing results, indicate that certain quats can act as asthmagens.” With regard to association studies between QAC exposure and asthma, the authors discussed methodological concerns, such as limited understanding of exposure pathways and an inability to quantify risk of

[6] Bellier et al. (2015) listed both of these chemical names, which can be used to describe the same compounds (see footnote 3), and did not specify alkyl chain lengths.

new-onset asthma attributable to the exposure. They also noted data gaps in quantitative exposure measurements.

In a cohort of female nurses from the Nurses' Health Study II, exposures to disinfectants and cleaning products were evaluated based on job tasks[7] (Dumas et al., 2019). "High-level exposures" to multiple products, including QAC-containing disinfectants were significantly associated with increased risk of chronic obstructive pulmonary disease (COPD) incidence, independent of asthma and smoking status. The study authors discussed that several exposures often occurred concurrently and that disentangling the role of each product was a challenge.

US EPA (2017b) summarized the results of a guideline subchronic inhalation toxicology study of didecyldimethyl ammonium chloride. Effects including ulceration of the nasal cavity and increased levels of lung inflammation markers were observed in rats administered the compound by nose-only exposure. A no-observed-adverse-effect concentration (NOAEC) was not established in this study; the lowest concentration tested was 80 $\mu g/m^3$ didecyldimethyl ammonium chloride.

Larsen et al. (2012) evaluated acute airway effects in mice after inhalation exposure to aerosols of selected QACs, to generate information on toxicological mechanisms and to support risk assessment of occupational exposures. All QACs tested reduced tidal volume with a concomitant increase in respiratory rate. The relative potencies for this effect were: benzalkonium chloride > hexadecyltrimethyl ammonium bromide = cetylpyridinium chloride > dioctadecyldimethyl ammonium bromide. Inhalation of benzalkonium chloride and cetylpyridinium chloride gave rise to pulmonary inflammation.

Kwon et al. (2019) studied the inhalation toxicity in rats of benzalkonium chloride[8] and triethylene glycol (TEG) aerosols, alone and in combination. They found that exposure to benzalkonium chloride aerosol induced pulmonary cell damage and inflammation. The combination of benzalkonium chloride and TEG induced significant ulceration and degenerative necrosis in the nasal cavities; pulmonary effects were not observed. The mass median aerodynamic diameter of the aerosol particles from aqueous solutions of benzalkonium chloride ranged from 1.3 micrometers (μm) (0.5% solution) to 1.4 μm (2% solution). When combined with TEG, particle sizes were somewhat larger (1.3-3.2 μm).

[7] A nurse-specific job task-exposure matrix (JTEM) was used to assign an exposure level of low, medium, or high based on both nursing job type and disinfection tasks.

[8] Kwon et al. (2019) noted that the four major benzalkonium chloride components had alkyl chain lengths of C10, C12, C14, and C16; exposure concentrations of these four compounds were combined and reported as total benzalkonium chloride.

Dinis-Oliveira et al. (2008) reviewed the lung toxicity of paraquat dichloride, which selectively accumulates in the lungs. This compound acts by a redox cycling mechanism of action in inducing irreversible loss of lung function.

Nervous system effects
ECHA reported that there was no evidence from guideline studies of neurotoxicity for either alkyldimethylbenzyl ammonium chloride (ECHA, 2015a) or didecyldimethyl ammonium chloride (ECHA, 2015b).

Diquat and paraquat exposures have been implicated in neurodegenerative diseases, such as Parkinson's disease (Magalhães et al., 2018; Zhang et al., 2016).

Reproductive and developmental effects
In a summary of guideline studies, US EPA (2017a) stated that there was no evidence of developmental toxicity following prenatal alkyldimethylbenzyl ammonium chloride administration to rats or rabbits. Reduced pup body weight during lactation and post-weaning was observed in rats administered the highest dose of alkyldimethylbenzyl ammonium chloride; no other reproduction or fertility effects were reported (US EPA, 2017a). US EPA (2017b) noted reduced pup body weight and weight gain in rats exposed to didecyldimethyl ammonium chloride. In their assessments of alkyldimethylbenzyl ammonium chloride (ECHA, 2015a) and didecyldimethyl ammonium chloride (ECHA, 2015b), ECHA stated that neither compound "affected reproduction or development at doses that were not toxic to the mother" in rodent studies. DPR (1996) reported no reproductive or teratogenic effects of didecyldimethyl ammonium chloride, which has been designated by US EPA as the representative chemical for toxicology studies for all DADMACs used as pesticides, including dioctyldimethyl ammonium chloride, octyldecyldimethyl ammonium chloride, and octyldodecyldimethyl ammonium chloride.

Decreased fertility was observed in mice housed in facilities where a disinfectant containing a mixture of alkyl (60% C14, 25% C12, 15% C16) dimethylbenzyl ammonium chloride and didecyldimethyl ammonium chloride was used (Melin et al., 2014). Melin et al. (2014; 2016) further explored this observation in a series of experiments in which mice were exposed to the same disinfectant via the diet. These studies found that exposed mice had significantly reduced fertility and fecundity, and displayed reproductive effects including females progressing through fewer estrus cycles, and decreased sperm count in males. Decreased sperm counts were also observed in male mice exposed only ambiently to the disinfectant used in the animal facility (Melin et al., 2016). Hrubec et al. (2017) conducted additional experiments in mice exposed to the same disinfectant via the diet, mice orally gavaged with a mixture of the pure QAC chemical constituents, and mice and rats exposed ambiently to the disinfectant used in the animal facility. This study reported developmental effects in both mice and rats

exposed to these QACs via all three exposure routes. These effects manifested as neural tube defects in early gestation and decreased pup size and survivability in late gestation (Hrubec et al., 2017). The neural tube defects persisted in mice for two generations after cessation of exposure, and male exposure alone was sufficient for observation of these defects (Hrubec et al., 2017). Hrubec and Hunt (2018) acknowledged that preventing ambient exposure to QAC-containing disinfectants in animal facilities was a challenge in these studies.

Herron et al. (2019) exposed mouse dams to benzyldodecyldimethyl ammonium chloride or benzylhexadecyldimethyl ammonium chloride via the diet and evaluated the effects on the neonatal pup brain. Both of these benzalkonium chlorides were detected in the neonatal brain tissues, indicating transfer across the placental and embryonic blood-brain barriers. The authors observed altered sterol and lipid homeostasis in the exposed neonatal pup brains.

Some QACs have historically been used in the US as the active compound in fertility control. In an *in vitro* screening of organic compounds, Holzaepfel et al. (1959) identified some QA salts as having high spermicidal activity, including benzylhexadecyldimethyl ammonium chloride, n-octadecyldimethylbenzyl ammonium chloride (C18), and alkyldimethylbenzyl ammonium chloride[9]. A US patent from the 1970s describes QACs (including BACs, DADMACs, ATMACs, and QAC mixtures) as having the capability of controlling fertility if administered at the time of mating or within an effective period after mating (Dalgard and Coval, 1975). This patent described dog and rat studies that indicated QACs administered via the diet may be embryocidal, ovicidal, and/or spermicidal. Benzalkonium chloride is used as the active spermicidal ingredient in some sponges and vaginal creams and capsules currently sold in Europe (Aubeny et al., 2000; Creatsas et al., 2001; Pharma GDD website, accessed 2020). Its spermicidal mechanism of action occurs through destruction of the sperm cell plasma membrane (Creatsas et al., 2001). Plasma membrane disruption is also the general mechanism of action by which QACs, including benzalkonium chloride, are effective as preservatives, disinfectants, and biocides (Gilbert and Moore, 2005; Wessels and Ingmer, 2013).

Magalhães et al. (2018) reviewed the reproductive and developmental effects of diquat in rodent studies, including intrauterine growth retardation in rats, delayed ossification in rabbits, and the role of redox cycling processes in decreased mouse litter size.

Exposures to either benzalkonium chloride or benzethonium chloride resulted in delayed hatching, embryonic mortality, and morphological malformations in zebrafish, and in germline toxicity in *C. elegans* (Sreevidya et al., 2017).

[9] Holzaepfel et al. (1959) stated that the alkyl groups are “probably” C12 to C18.

Rat studies of dermally applied distearyldimethyl ammonium chloride, benzylstearyldimethyl ammonium chloride (C18), or stearyltrimethyl ammonium chloride identified no embryotoxic effects (Palmer et al. 1983).

Immunological effects

The NIOSH study (Anderson et al., 2016) discussed on page 7 above also linked markers of immune sensitization to the development of skin irritation and allergic sensitization observed in mice dermally exposed to didecyldimethyl ammonium chloride. McDonald (2017 dissertation) found that a mixture of alkyl (60% C14, 25% C12, 15% C16) dimethylbenzyl ammonium chloride and didecyldimethyl ammonium chloride altered cytokine levels and phagocytic function *in vitro*, and affected antibody production and the gut microbiome in mice.

Sanidad et al. (2018) reported that benzalkonium chloride and benzethonium chloride increased inflammation in a mouse model of induced colitis. These chemicals also caused a reduction in colon length, which is a biomarker of colitis. In another experiment using a mouse model of induced colon cancer, the authors found that treatment with benzalkonium chloride increased tumor size and increased the gene expression of several pro-tumorigenic genes in colon tumors. They also found that benzalkonium chloride increased activation of an innate immunity receptor (Toll-like receptor 4).

Altered cellular function and effects on metabolism

Benzalkonium chloride[10] (Datta et al., 2017a), cetylpyridinium chloride (Datta et al., 2017b), and decyltrimethyl ammonium bromide (Inácio et al., 2013) inhibited mitochondrial respiration *in vitro*. Levine et al. (2007) reported that benzalkonium chloride's disruption of mitochondrial function inhibits steroidogenesis in Leydig cells. Datta et al. (2017b) observed anti-estrogenic activity of cetylpyridinium chloride *in vitro*, and hypothesized that this is mediated through effects on mitochondrial inhibition.

Decyltrimethyl ammonium bromide induced the generation of intracellular reactive oxygen species, particularly superoxide anion (Inácio et al., 2013). Diquat and paraquat are also known to produce reactive oxygen and nitrogen species through redox cycling processes (Dinis-Oliveira et al., 2008; Magalhães et al., 2018).

Herron et al. (2016) reported inhibition of cholesterol biosynthesis in *in vitro* studies of benzalkonium chlorides. The authors suggested that this effect decreased with increasing length of the alkyl chain; benzyldecyldimethyl ammonium chloride (C10) was a more potent cholesterol biosynthesis inhibitor than benzylhexadecyldimethyl ammonium chloride (C16). In additional *in vitro* studies, benzyldecyldimethyl ammonium

[10] Datta et al. (2017a) describe benzalkonium chloride as a mixture of alkyl chain lengths with 8, 10, 12, 14, 16, or 18 carbons; they do not identify the specific compounds tested.

chloride and benzylhexadecyldimethyl ammonium chloride differentially altered lipid homeostasis (Hines et al., 2017).

We searched US EPA's Chemistry Dashboard (Williams et al., 2017) for QAC bioactivity data in ToxCast/Tox21 assays. 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 sub-cytotoxic concentrations include: dodecyltrimethyl ammonium chloride's effects on receptor binding (e.g., G protein-coupled receptors) and altered cell proliferation, N,N,N-trimethyloctadecan-1-aminium chloride's impact on altered gene expression, and ethylhexadecyldimethyl ammonium bromide's effects on enzyme activity (e.g., increased enzymatic activity of selected cytochrome P450s), gene expression, and cell morphology.

Potential to biomonitor

Chemical properties

QACs are generally described as highly water soluble, but the reported solubility can vary substantially by chain length. For example, the estimated water solubilities for dodecyltrimethyl ammonium bromide (an ATMAC with a C12 chain) and docosyltrimethyl ammonium chloride (an ATMAC with a C22 chain) are 996 mg/L and 0.017 mg/L, respectively (Becker et al., 2012). As another example, the estimated water solubilities for dioctyldimethyl ammonium chloride (a DADMAC with C8 chains) and dioctadecyldimethyl ammonium chloride (a DADMAC with C18 chains) are 8,100 mg/L and 2.7 mg/L, respectively (Boethling, 1994).

OEHHA (2012) specified a log octanol-water partition coefficient (log K_{ow}) of ≥ 4 as indicating potential for bioaccumulation. Of those located, most log K_{ow} values for QACs are below 4 (Boethling, 1994; Kaj, et al. 2014; US EPA, 2017a; Ying, 2006). Kaj et al. (2014) reported a log K_{ow} of 4.26 for octadecyltrimethylammonium chloride. US EPA (2017b) reported a log K_{ow} of 4.66 for didecyldimethyl ammonium chloride, and stated that bioconcentration in aquatic organisms is not expected because this compound "is highly soluble in water and, being a positively-charged compound, is tightly sorbed to soil and sediment, which are typically negatively-charged."

We located limited information on experimentally measured bioconcentration factors (BCFs). OEHHA specified a BCF above 1,000 as an indicator used to evaluate potential for bioaccumulation. Kaj et al. (2014) reported a BCF of 1,962 for an ATMAC mixture of hexadecyltrimethylammonium chloride (C16) and octadecyltrimethylammonium chloride (C18) in fathead minnow. Other reported QAC BCFs located were below 1,000 (ECHA, 2015a; ECHA, 2015b; Kaj, 2014).

Environmental fate

QACs are strongly sorbed by a wide variety of materials, notably soils and sewage-affected sediments (Boethling, 1994; Kahrilas et al., 2015; Mulder et al., 2018; Zhang et al., 2015). US EPA reported that alkyldimethylbenzyl ammonium chloride (US EPA, 2017a) and didecyldimethyl ammonium chloride (US EPA, 2017b) are expected to be immobile in soil and sediment. ECHA stated that alkyldimethylbenzyl ammonium chloride (ECHA, 2015a) and didecyldimethyl ammonium chloride (ECHA, 2015b) can be considered immobile in various soil types.

Doherty (2013 dissertation) reviewed and summarized many studies on the degradation of QACs once released from sewage outfalls. Biodegradation under aerobic conditions is suggested to be the greatest for ATMACs, followed by BACs, and then DADMACs. The level of degradation is inversely proportional to the QAC alkyl chain length, and the major degradation pathway is thought to be via n-dealkylation at the C-N bond. Studies indicate that mono-, di-, and trialkylamine intermediates are not persistent, and that once primary biodegradation occurs, complete degradation should occur rapidly. Limited studies have generally found minimal or no degradation of QACs under anaerobic conditions. Doherty (2013 dissertation) summarized conflicting reports on whether QACs biodegrade while adsorbed onto sediments, and concluded from the reported experiments that longer chain QACs, such as dioctadecyldimethyl ammonium chloride, are especially persistent in sewage-affected sediments.

Boethling (1994) reported that greater than 70% of benzyltetradecyldimethyl ammonium chloride was removed during wastewater treatment in the US, and at least 90% of other monitored QACs were removed during treatment. A more recent Austrian study found that at least 90% of monitored BACs, DADMACs, and ATMACs were removed during treatment (Clara et al., 2007). Lara-Martín et al. (2010) and Li et al. (2018) indicated that QAC removal in WWTPs is thought to be dominated by both sorption to sludge and microbial degradation, except for longer chain DADMACs, which do not appreciably biodegrade during wastewater treatment due to their strong sorption to solids and their hydrophobicity.

Absorption

Dermal absorption rates for QACs have generally been reported to be low. Becker et al. (2010; 2012) reported dermal absorption of 1-2% forty-eight hours after rats were exposed to quaternium 15 and less than 1.5% twenty-four hours after rats were exposed to polyquaternium 10. ECHA (2015a) described an *in vitro* study with human skin that estimated dermal absorption of 8.3% for alkyldimethylbenzyl ammonium chloride.

Reported oral absorption rates are higher than dermal absorption rates. Rat studies of quaternium 15 found 84-88% absorption of quaternium 15 forty-eight hours after oral

administration (Becker et al. 2010). The Human and Environmental Risk Assessment (HERA) project in Europe summarized studies of three different esterquat groups, which found that absorption ranged from 40-73% following oral gavage in rats (HERA, 2009). ECHA (2015a; 2015b) reported 10% absorption in mammals (species not provided) following oral administration of alkyldimethylbenzyl ammonium chloride and of didecyldimethyl ammonium chloride (ECHA, 2015b).

Estimates of inhalation absorption rates were not located. In their safety assessment of quaternium 15, the Cosmetic Ingredient Review stated: “The mean particle diameter is about 38 µm in a typical aerosol spray [citing Johnsen, 2004]. In practice, aerosols should have at least 99% of particle diameters in the 10 to 110 µm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable” (Becker et al., 2010; see also their evaluation of trimoniums in Becker et al., 2012). Kwon et al. (2019) reported that aerosol particle sizes from aqueous solutions of benzalkonium chloride ranged from 1.3 µm (0.5% solution) to 1.4 µm (2% solution); when combined with TEG, particle sizes were somewhat larger (1.3-3.2 µm). Studies of inhalation exposures to certain QAC aerosols in rodents reported respiratory effects (Kwon et al., 2019; Larsen et al., 2012; US EPA, 2017b).

Metabolism

Metabolism information summarized by regulatory bodies for selected QACs indicates that the majority of the administered dose is eliminated in the feces (ECHA, 2015a; ECHA, 2015b; US EPA, 2006a; US EPA, 2006b). In rat metabolism studies, the major urinary metabolites of diethyloxyesterdimethyl ammonium chloride were dimethyldiethanol ammonium chloride (i.e., the de-esterification metabolite), as well as possibly some further oxidation products (summarized by HERA, 2009). In a summary of an unpublished Dow study, the Cosmetic Ingredient Review reported that formic acid was tentatively identified as a metabolite of quaternium 15, which is a known formaldehyde releaser (Becker et al., 2010).The same study also found evidence of several other metabolites in rat urine, but was unable to identify the compounds.

US EPA (2006b; 2017b) described a rat metabolism study in which most of the administered didecyldimethyl ammonium chloride was excreted in the feces, principally as the parent compound and four major metabolites that “were identified as oxidation products with oxidation confined to the decyl side chains.”

Experiments conducted with human liver microsomes identified various hydroxylated metabolites of benzalkonium chloride, produced primarily by the cytochrome P450 isoforms CYP2D6, CYP4F2, and CYP4F12 (Seguin et al., 2019).

Past biomonitoring studies

The only published human biomonitoring studies located were on diquat and paraquat.

Maroni et al. (2000) reviewed and summarized biomonitoring information for agricultural workers handling diquat dibromide and paraquat dichloride. No detectable urinary diquat (LOD: 0.047 mg/L) was observed in workers dermally exposed at levels ranging from 0.17-1.82 mg/hr and from personal air concentrations lower than 0.01 mg/hr. Urinary paraquat concentrations in workers exposed during normal agricultural use was generally lower than 0.01 mg/L. High urinary paraquat concentrations were detected in unprotected Thai spraymen (n = 14); concentrations ranged from 0.21-0.73 mg/L after fourteen days of spraying.

Posecion et al. (2008) evaluated meconium samples collected from infants (n = 70) born to mothers who resided near a banana plantation in the Philippines, where paraquat was sprayed. Of the meconium samples analyzed, paraquat was detected in two at concentrations of 106 ng/g and 46 ng/g, respectively (LOD: 15.6 ng/g).

Some papers relevant to biomonitoring methods for other QACs are available. For example, Herron et al. (2019) measured benzyldodecyldimethyl ammonium chloride and benzylhexadecyldimethyl ammonium chloride in blood from mice exposed via the diet. Major hydroxylated metabolites of these QACs were also detected in blood; some of the same metabolites were also identified *in vitro* (Seguin et al., 2019).

Analytical considerations

The analytical considerations specified in the criteria for designated chemicals are:

- Availability of a biomonitoring analytical method with adequate accuracy, precision, sensitivity, specificity, and speed.
- Availability of adequate biospecimen samples.
- Incremental analytical cost to perform the biomonitoring analysis for the chemical.

Adequate biospecimens (i.e., blood and/or urine) would be available. Biomonitoring California would have to develop methods to measure QACs in future studies, which would require additional laboratory resources.

Need to assess efficacy of public health actions

The importance of evaluating human exposure to QACs and concerns about potential effects of these compounds have been raised by a number of groups.

Health Canada (2018) initiated action on QACs under its Chemicals Management Plan by issuing a notice to collect information on quantities, concentrations, and uses from manufacturers and importers. This applies to approximately 800 chemicals identified as QACs. The purpose is to establish an up-to-date inventory that can be used to inform risk assessment and risk management.

Merchel Piovesan Pereira and Tagkopoulos (2019) reviewed the regulatory status of benzalkonium chlorides, noting some recent changes in the European Union (EU). Maximum residue levels of these compounds allowed in food products were lowered from 0.5 mg/kg to 0.1 mg/kg. The review stated that the EU has also withdrawn approval for the use of benzalkonium chlorides in "several biocidal products, such as consumer hand and body wash antiseptics, which is in contrast with current legislation in the United States."

Merchel Piovesan Pereira and Tagkopoulos (2019) also examined the issue of microbial resistance, concluding that "the ubiquitous and frequent use of BACs [benzalkonium chlorides] in commercial products can generate selective environments that favor microbial phenotypes potentially cross-resistant to a variety of compounds." Han et al. (2019) studied the role QACs could play in the transmission of antibiotic resistant genes in experiments with several compounds. They concluded that "QACs could promote the evolution of bacterial resistance to multiple antibiotics" and recommended further investigation.

Holm et al. (2019) discussed QACs in their review of the efficacy and health risks associated with disinfectants used in child care sites, raising concerns about various health effects, including the asthmagenicity and potential reproductive toxicity of some of these compounds. They concluded based on their review that "peroxide products are preferable when other factors are equal, because they have less respiratory toxicity than bleach or quaternary ammonias. Peroxides also do not present the same concerns for reproductive toxicity that the quats do."

The California Council on Science and Technology (CCST) and the Lawrence Berkeley National Laboratory (LBNL) conducted an assessment of oil and gas well stimulation in California (CCST and LBNL, 2015). Their discussion of certain chemical classes used in hydraulic fracturing, including QACs, is excerpted below:

> "A few classes of chemicals used in hydraulic fracturing (e.g. biocides, quaternary ammonium compounds, etc.) present larger hazards because of their relatively high toxicity, frequent use, or use in large amounts. The environmental characteristics of many chemicals remain unknown. We lack information to determine if these chemicals would present a threat to human health or the environment if released to groundwater or other environmental media. Application of green chemistry principles, including reduction of hazardous chemical use and substitution of less hazardous chemicals, would reduce potential risk to the environment or human health."

Pellizari et al. (2019) reviewed QACs in their prioritization of chemicals for biomonitoring; extensive data gaps in exposure and toxicity information were noted. The

authors recommended the development of biomarkers and obtaining additional toxicity data for selected QACs.

Adding QACs as a class to Biomonitoring California's list of designated chemicals would allow any member of the class to be considered for a future study. Results from biomonitoring studies could help address the knowledge gaps related to human exposure to these widely used compounds, and inform efforts to reduce chemical exposures of concern.

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