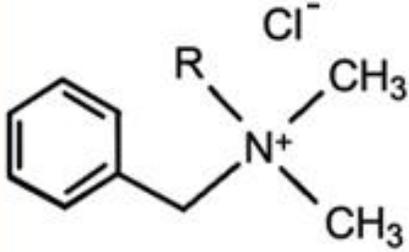


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<p>CAS #: 68424-85-1 Representative CAS # for ADBAC</p> 	<p>NAME: Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Synonym¹s: n-alkyl (C14 50%; C12 40%; C16 10%) dimethyl benzyl ammonium chloride; Alkyl(C12-16)dimethylbenzylammonium chloride; Ammonium, alkyl(C12-C16)dimethylbenzyl-, chlorides; Barquat MB 80; Benzyl-C12-C16-alkyldimethyl ammonium chlorides; Bioquat 501; Bioquat 80; Black alg aetrine; BTC 835; Catigene T80; Cyncal 80; EINECS 270-325-2; Gardiquat 1250AF; Hyamine 3500; Maquat MC 1412; Protek Q; Rolquat cdm/BC; Tret-O-lite WF 828; Tret-O-lite WF 88; C12-16-Alkyldimethylbenzylammonium chloride RTECS #¹: UZ2995000 EINECS #²: 270-325-2 Molecular Weight³: 377.83 Molecular Formula⁴: RC₉H₁₃NCl R= n-alkyl (C₁₂ 40%, C₁₄ 50%, C₁₆ 10%) EPA PC Code⁴: 069105 Related CAS #'s: (See list at end of summary)</p>
PHYSICAL CHARACTERISTICS	
<p><i>Primary Use</i></p>	<p>ADBAC is an antimicrobial used in agricultural, food handling, commercial/ institutional/ industrial, residential and public access, and medical settings⁴.</p> <p>There are 667 EPA-registered products that contain ADBAC as an active ingredient, 664 of which are registered as antimicrobial products and 3 that are conventional products. Production volume data for the years 2011 through 2014 indicate that approximately 198 million pounds of ADBAC are sold per year in the United States³.</p> <p>“Due to their amphiphilic nature, QACs act as detergents or surface-active agents against microorganisms. QACs target bacterial cell membranes through electrostatic interactions between the positively charged head group and negatively charged cytoplasmic membrane, adsorption, and then permeation of side chains into the intramembrane region. The lipid layer of enveloped viruses makes them sensitive to the hydrophobic activity of QACs” (Hora, 2020)⁵.</p>
<p><i>Physical state, odor at room temperature & pressure</i></p>	<p>Crystalline sold in pure form Clear yellow to straw colored liquid with an amine odor⁴</p>
<p><i>Melting point; Boiling point</i></p>	<p>MP: 241.02°C BP: 560.84°C⁴</p>
<p><i>Solubility</i></p>	<p>Soluble in water and alcohols³ 2.2 mg/L at 25°C⁶</p>

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<i>Specific Gravity</i>	
SAFETY/PHYSICAL HAZARDS	
<i>Vapor Pressure</i>	3.53x 10 ⁻¹² mm Hg ⁴
<i>Flammability</i>	
<i>Flashpoint</i>	
<i>Flammability Rating</i>	
<i>Auto Ignition Point</i>	
<i>Combustion products</i>	
<i>Explosivity (UEL, LEL, shock sensitive)</i>	
<i>Oxidizer</i>	
<i>Corrosivity</i>	<p>Industrial Concentrates: 50-80% of active QAC ingredient. Acute Tox, Inhalation – Category 2 Skin Corrosion/Irritation – Category 1 Serious eye damage/eye irritation – Category 1 Hazardous to the aquatic environment, acute & chronic hazard – Cat 1</p> <p>Ready-to-use Products: .08-20% of active QAC ingredient. Skin corrosion/irritation – Category 2 Serious eye damage/eye irritation – Category 1</p>
<i>pH</i>	7.59 ⁴
<i>Reactivity</i>	
<i>Viscosity</i>	
<i>Odor Threshold</i>	
<i>Particle size, shape, respirable fraction</i>	
<i>Other physical hazards associated with process: Heat, gases under pressure, noise, vibration, ergonomic hazard</i>	
HEALTH HAZARDS	
Acute Toxicity	
<i>Oral LD₅₀</i>	LD ₅₀ Rat = 304.5 mg/kg (combined) LD ₅₀ Rat = 510.9 mg/kg (males) 280.8 mg/kg (females) ⁴ EPA Toxicity Category II ⁴
<i>Dermal LD₅₀</i>	LD ₅₀ Rat = 930 mg/kg (combined) LD ₅₀ Rat = 1100 mg/kg (males) 704 mg/kg (females) ⁴ EPA Toxicity Category III ⁴
<i>Inhalation LC₅₀</i>	0.054 < LC ₅₀ (Rat) < 0.51 mg/L ⁴ EPA Toxicity Category II ⁴

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<i>Intraperitoneal LD₅₀</i>	
Chronic or Sub-chronic Toxicity	
<i>IARC rating</i>	
<i>Carcinogenicity</i>	
<i>Neurotoxicity</i>	<p>“The goal of this study was to use targeted and untargeted mass spectrometry and transcriptomics to investigate the effect of BACs on sterol and lipid homeostasis and to predict the mechanism of toxicity of BACs on neurodevelopmental processes. After maternal dietary exposure to 120mg BAC/kg body weight/day, we quantified BAC levels in the mouse neonatal brain, demonstrating for the first time that BACs can cross the blood-placental barrier and enter the developing brain. Transcriptomic analysis of neonatal brains using RNA sequencing revealed alterations in canonical pathways related to cholesterol biosynthesis, liver X receptor-retinoid X receptor (LXR/RXR) signaling, and glutamate receptor signaling. Mass spectrometry analysis revealed decreases in total sterol levels and downregulation of triglycerides and diglycerides, which were consistent with the upregulation of genes involved in sterol biosynthesis and uptake as well as inhibition of LXR signaling. In conclusion, these findings demonstrate that BACs target sterol and lipid homeostasis and provide new insights for the possible mechanisms of action of BACs as developmental neurotoxicants.”⁷</p> <p>“Significantly, even at non-cytotoxic concentrations, BACs can potentially inhibit Dhcr7. This suggests that exposure of BACs could have severe consequences even when there is no apparent acute toxicity. It has been reported that orally administered BAC can cross the blood-brain barrier in rats (a 1.2 lg/g concentration in serum leads to 0.2 lg/g in brain) (Xue et al., 2002, 2004), which suggests that BAC could pose threat to the central nervous system.”⁸</p>
<i>Developmental/Reproductive Toxicity</i>	<p>“Decreased reproductive performance in laboratory mice coincided with the introduction of a disinfectant containing both ADBAC and DDAC. QACs were detected in caging material over a period of several months following cessation of disinfectant use. Breeding pairs exposed for six months to a QAC disinfectant exhibited decreases in fertility and fecundity: increased time to first litter, longer pregnancy intervals, fewer pups per litter and fewer pregnancies. Significant morbidity in near term dams was also observed.”⁹</p> <p>“Breeding pairs exposed for six months to a QAC disinfectant exhibited decreases in fertility and fecundity: increased time to first litter, longer pregnancy intervals, fewer pups per litter and fewer pregnancies.</p>

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Significant morbidity in near term dams was also observed. Exposure to a common QAC disinfectant mixture significantly impaired reproductive health in mice. The study demonstrated that ADBAC + DDAC exposure is toxic to both male and female fertility. Female mice exposed to ADBAC + DDAC exhibited decreased reproductive capacity with reduced ovulation and fewer estrus cycles. Male mice exposed to ADBAC + DDAC exhibited significantly decreased sperm concentration and motility.”¹⁰

Neural tube defects (NTD) were seen in both rats and mice following ambient exposure to the QAC’s containing disinfectant in the mouse room. NTDs were also observed in mice dosed with the disinfectant at 60 or 120 mg/kg/day in feed, or with ADBAC+DDAC chemical by gavage at 7.5, 15, or 30 mg/kg/day. Mice received ambient exposure for 2 weeks or ambient and gavage. NTDs were seen with ADBAC and DDAC dosed acutely by oral gavage, chronically in feed, and ambiently through the use of disinfectant in the mouse room. Both ambient and ambient and gavage groups exhibited significantly increased levels of NTDs compared with unexposed controls (Hrubec, 2017).¹¹

Note also QAC industry critique of Hrubec 2017 study¹²

“The effects of the spermicide benzalkonium chloride (BKC) were studied on the conceptus of rat. Single doses (0, 25, 50, 100 or 200 mg kg-1) of aqueous solutions of BKC were administered intravaginally (1 ml kg-1) on gestational day 1. The vulval metallic clips, used to prevent leakage of the solution, were removed 24 h post-treatment. Fetuses were obtained and examined for malformations on day 21 of gestation. Slight to copious amounts of vaginal discharge and vaginitis were noticed in rats treated with the two largest doses of BKC. **A dose-related increase in resorptions and fetal death, reduction in litter size and weight were observed in BKC-treated dams.** The conceptus loss seemed to occur both before and after implantation. BKC did not cause any discernible visceral malformations, although minor sternal defects occurred in fetuses exposed to 100 and 200 mg kg-1 of the spermicide. These results suggest that single vaginal application of BKC is embryo- and fetocidal in the rat at a dose about 143 times higher than that recommended for controlling conception in women.”¹³

“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

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high spermicidal activity, including benzylhexadecyldimethyl ammonium chloride, n-octadecyldimethylbenzyl ammonium chloride (C18), and alkyldimethylbenzyl ammonium chloride. 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, ovidal, 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).”¹⁴

“The prenatal developmental toxicity potential of ADBAC and DDAC was evaluated in regulatory compliant studies. Pregnant female CD[®] rats (25/group) and New Zealand White rabbits (16/group) were administered ADBAC (0, 10, 30 or 100 mg/kg/day and 0, 1, 3 or 9 mg/kg/day, respectively), or DDAC (0, 1, 10 or 20 mg/kg/day and 0, 1, 3 or 10 mg/kg/day, respectively), by oral gavage on gestation days (GD) 6-15 for rats and GD 6-18 for rabbits. At scheduled termination (GD 21 for rats; GD 29 for rabbits), maternal necropsies were conducted and live fetuses were weighed and examined for external, visceral, and skeletal malformations and variations. Clinical signs of maternal toxicity were observed in rats and rabbits dosed with ADBAC, resulting in no-observed-adverse-effect levels (NOAELs) of 10 and 3 mg/kg/day, respectively. Despite the treatment-related maternal toxicity of ADBAC, the NOAEL for prenatal developmental toxicity was 100 and 9 mg/kg/day for rats and rabbits, respectively, the highest doses evaluated. Repeated oral doses of DDAC resulted in maternal toxicity in both species at the top two doses, with 25% mortality noted in rabbits at 10 mg/kg/day. No teratogenic effects were observed at any dose for either species. However, increased incidence of dead fetuses per litter and decreased fetal body weights were observed in rabbits at the maternally lethal dose of 10 mg/kg/day. The NOAEL for maternal toxicity of DDAC was 1 mg/kg/day for both species and the NOAEL for

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	<p style="color: red;">prenatal developmental toxicity was 20 and 3 mg/kg/day, for rats and rabbits, respectively.”¹⁵</p>
<i>Genotoxicity/Mutagenicity</i>	<p>“We tested two important representatives, namely, benzalkonium chloride (BAC) and dimethyldioctadecyl-ammonium bromide (DDAB) in four genotoxicity tests. With BAC, a moderate but significant effect was found with an exposure concentration of 1.0 mg/l while DDAB caused damage at lower doses (0.3 mg/l). Our findings show that both chemicals induce moderate but significant genotoxic effects in eukaryotic cells at concentrations which are found in wastewaters and indicate that their release into the environment may cause genetic damage in exposed organisms. Furthermore, the direct contact of humans to QAC-containing detergents and pharmaceuticals that contain substantially higher concentrations than those which were required to cause effects in eukaryotic cells in the present study should be studied further in regard to potential DNA-damaging effects in man (Ferk, 2007).”¹⁶</p>
<i>Endocrine Disruption</i>	<p>Females exposed to ADBAC + DDAC demonstrated significantly decreased ovulatory capacity, spent less time in estrus, and progressed through fewer estrus cycles compared to controls. It is, therefore, conceivable that ADBAC + DDAC reduced estrus length and frequency through disruption of estrogen-regulated processes. ADBAC + DDAC treated mice had significantly fewer estrus cycles over the evaluation period. This correlates directly with our 6 month breeding trial which observed significantly fewer litters produced in ADBAC + DDAC treated mice. These two findings reinforce that ADBAC + DDAC disrupt reproductive function in female mice (Melin, 2016).¹⁷</p> <p style="color: red;">“Based on a thorough review of all identified data pertinent to the potential endocrine activity and ED-mediated adversity of ADBAC, it is concluded that the substance is not an endocrine disruptor according to the criteria laid down in Regulation (EU) 2018/605. There is no evidence for ADBAC to cause adverse effects as a consequence of an endocrine mode of action.”¹⁸</p> <p style="color: red;">Alkyl (C12-16) dimethylbenzyl ammonium chloride does not fulfil criterion (d) of Article 5(1) and is not considered an endocrine disruptor by the EU.¹⁹</p> <p style="color: red;">See Excel download of EPA Comp Tox Data with active endocrine disruption assays listed.</p>
<i>Thyroid</i>	
<i>Immunotoxicity</i>	<p>“This study demonstrates that the Th2-dependent adjuvanticity of</p>

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	QACs requires a minimum length of the alkyl chains. The adjuvant effect was not related to the suppressive effect on antibody production. Simultaneous administration of TEA, a QAC without adjuvant effect, and DDA, a QAC with adjuvant effect, increased the adjuvanticity. This may be of practical importance, since many QAC-containing products contain mixtures of several QACs.” ²⁰
<i>Liver</i>	
<i>Other organ toxicity</i>	“Kinetic characteristics and toxic effects of benzalkonium chloride (BZK) following injection via jugular vein (JV), femoral artery (FA) and oral administration (PO) were experimentally investigated using rats. The BZK concentrations in blood and tissues (lung, liver and kidney) were determined by high-performance liquid chromatography with solid phase extraction. Toxic doses of 15 and 250 mg/kg of BZK were used for intravascular (JV and FA) and PO administration, respectively. The fatal effects appeared soon after the dose in JV-rats, while delayed in FA- or PO-rats. The blood BZK concentrations and the elimination half-lives were similar between JV- and FA-rats, while the distribution of BZK in tissues was slightly different. In PO administration, the rats that aspirated BZK into their lungs had some symptoms, while the rats that did not aspirate BZK appeared to be normal. The BZK concentrations in blood and tissues were significantly higher in the aspirated PO-rats. The toxic degree of BZK was correlated with the BZK concentration in orally dosed rats. Lung and kidney had higher BZK concentrations compared to blood or liver, and they could be the target organs of BZK.” ²¹
Skin, Eye and Respiratory Effects	
<i>Irritant – Skin, Eye, or Respiratory</i>	“Our study showed BAK to be an allergen of increasing importance. From 1998 through 2000, 2001 through 2005, and 2006 through 2010, the rate of allergic patch test results to BAK increased. More than half of the reactions in each period studied were graded as macular erythema, with at least one third of all reactions deemed to be relevant. Irritancy rates were consistently low (Wentworth, 2016).” ²² “This analysis of routine clinical data and a number of previous reports add further, if weak, evidence to the notion that BAC is a contact allergen, albeit a very rare one (Uter, 2008).” ²³
<i>Corrosive – S, E, or R</i>	Skin Corr. 1B; H314: causes severe skin burns and eye according to CLP (EC 1272/2008) criteria. Rabbit eye using undiluted test substance produced severe and irreversible damage in rabbit eyes (Wallace, 1975). ²⁴
<i>Permanent Damage – S, E, or R</i>	
<i>Sensitizer – S & R</i>	“Hypersensitivity to benzalkonium chloride was asserted by allergologic

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	<p>exploration in the three cases reported. Contact allergy, a frequent phenomenon, was diagnosed in two cases. The third case represents one of the few cases described in ophthalmology of immediate hypersensitivity associated to vital risk: chemosis and angioneurotic edema is reported in a woman who had been already presented an anaphylactic shock to a quaternary ammonium family anaesthetic (Chiambaretta, 1997).”²⁵</p>
<p><i>Asthmagen – Initiator or Exacerbator</i></p>	<p>AOEC: Ashthmagen (Rs) – sensitizer-induced²⁶</p> <p>Two papers were cited to support this conclusion (Bernstein et al, 1994; Purohit et al, 2000).</p> <p>“Exposure to QACs increased significantly the risk of reported physician-diagnosed asthma and nasal symptoms at work (adjusted OR = 7.5 and 3.2, respectively). No significant association was found with other exposures such as latex glove use, chlorinated products/bleach or glutaraldehyde”.²⁷</p> <p>“The three patients in this study, all of which were female nurses manifested asthma symptoms upon handling disinfectant solutions containing benzalkonium chloride. Work-related fall in PEFR (Peak expiratory flow rate) was observed in all of them. The diagnosis was confirmed by challenge tests where the patients were exposed, in a closed chamber, to suspected disinfectant contained in a tray. All of the women developed early or delayed symptoms upon exposure. Similar challenge tests to placebo or other disinfectants devoid of quaternary ammonium compound were negative (Purohit, 2000).”²⁸</p> <p>“We describe a case of occupational asthma caused by prolonged exposure to a cleaning solution containing benzalkonium chloride in the workplace. Single-blind, placebo-controlled, open-room challenges were performed to determine the specific agent responsible for the patient’s symptoms. Pulmonary function and epicutaneous challenge tests were also performed. The patient had positive responses to challenges with a liquid toilet bowl cleaner containing benzalkonium chloride but was unreactive to other agents tested. Removal from the workplace resulted in complete resolution of symptoms. The exact mechanisms responsible for occupational asthma induced by quaternary amines remain unknown; however; this case emphasizes the importance of recognizing reactive chemicals as possible causes²⁹.”</p> <p>Benzalkonium chloride is used as a preservative in some multidose</p>

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nebulized bronchodilators. BACs bronchoconstrictive properties in relation to this use are well documented.³⁰

“Challenge exposure to the suspected cleaning agents elicited a $\geq 20\%$ fall in forced expiratory volume in 1 s (FEV1) in 17 (39%) participants. The cleaning products that induced a positive specific inhalation challenge (SIC) contained quaternary ammonium compounds (n=10), glutaraldehyde (n=3), both of these agents (n=1) and ethanolamines (n=2). Positive SICs were associated with a significant decrease in the median (IQR) value of the provocative concentration of histamine causing a 20% fall in FEV1 (PC20) from 1.4 (0.2–4.2) mg/mL at baseline to 0.5 (0.4–3.0) mg/mL after the challenge and a significant increase in sputum eosinophils from 1.8 (0.8–7.2)% at baseline to 10.0 (4.1–15.9)% 7 h after the challenge exposure while these parameters did not significantly change in participants with a negative SIC. Overall, 11 of 17 participants with positive SICs showed greater than threefold decrease in post challenge histamine PC20 value, a $>2\%$ increase in sputum eosinophils, or both of these outcomes. Conclusions: **These data indicate that a substantial proportion of workers who experience asthma symptoms related to cleaning materials show a pattern of bronchial reaction consistent with sensitiser-induced occupational asthma. The results also suggest that quaternary ammonium compounds are the principal cause of sensitiser-induced occupational asthma among cleaners.**”³¹

“BAC (4.1–4.5 mg/m³, sprayed from 0.5% solution) promoted pulmonary cell damage and inflammation as depicted by the increase in total protein, lactate dehydrogenase, polymorphonuclear leukocytes, and macrophage inflammatory protein-2 in the bronchoalveolar lavage fluid.”³²

“High-level exposure, evaluated by the JTEM, to several specific disinfectants (ie, glutaraldehyde, bleach, hydrogen peroxide, alcohol, and quaternary ammonium compounds) was significantly associated with COPD incidence, with adjusted hazard ratios ranging from 1.25 (95% CI, 1.04-1.51) to 1.36 (95% CI, 1.13-1.64). Associations were not modified by smoking or asthma status (P for interaction $> .15$).”³³

“Weekly use of disinfectants to clean surfaces only (23% exposed) or to clean medical instruments (19% exposed) was not associated with incident asthma (adjusted hazard ratio [95%CI] for surfaces, 1.12 [0.87–

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	<p>1.43]; for instruments, 1.13 [0.87–1.48]).”³⁴</p> <p>“Atopic sensitization (defined as increased production of IgE to common allergens) was found to occur more frequently in farmers who used disinfectants containing quaternary ammonium compounds (QACs) (odds ratio (OR) 7.4; 95% confidence interval (95% CI) 1.3–43.1).”³⁵</p> <p>“The onset or aggravation of asthma in this group could be related to an irritant-induced mechanism or to specific sensitization. The main sensitizers contained in cleaning products are disinfectants, quaternary ammonium compounds (such as benzalkonium chloride), amine compounds, and fragrances.”³⁶</p> <p>“The QACs gave rise to concentration-dependent decreases in the tidal volume (VT) and a concomitant increase in respiratory rate indicating pulmonary irritation. The potencies of the QAC to induce these effects were in the order: BAC > HTA = CPC > DDA. Furthermore, inhalation of BAC and CPC aerosols gave rise to pulmonary inflammation as apparent from bronchoalveolar lavage.”³⁷</p>
<i>Skin Absorption, Kp</i>	
<i>LOAEL</i>	<p>Inhalation LOAEC < 0.08 mg/m³</p> <p>Chronic Dietary (Rat) – 88 mg/kg/day</p> <p>Incidental Oral (Rat) – 30 mg/kg/day⁴</p>
<i>NOAEL</i>	<p>Chronic Dietary (Rat) – 44 mg/kg/day</p> <p>Incidental Oral (Rat) – 10 mg/kg/day</p> <p>Short-Term Dermal (Guinea Pigs) – 20 mg ai/kg/day⁴</p>
<i>Benchmark Dose Response (BMD)</i>	
<i>Toxicokinetics</i>	<p>“In this study, we aim to identify environmental molecules that can inhibit cholesterol biosynthesis, potentially leading to the same biochemical defects as observed in cholesterol biosynthesis disorders, which are often characterized by congenital malformations and developmental delay. Using the Distributed Structure-Searchable Toxicity (DSSTox) Database Network developed by EPA, we first carried out in silico screening of environmental molecules that display structures similar to AY9944, a known potent inhibitor of 3b hydroxysterol-D7-reductase (DHCR7)—the last step of cholesterol biosynthesis. Molecules that display high similarity to AY9944 were subjected to test in mouse and human neuroblastoma cells for their effectiveness in inhibiting cholesterol biosynthesis by analyzing cholesterol and its precursor using gas chromatography-mass</p>

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spectrometry. We found that a common disinfectant mixture, benzalkonium chlorides (BACs), exhibits high potency in inhibiting DHCR7, as suggested by greatly elevated levels of the cholesterol precursor, 7-dehydrocholesterol (7-DHC). Subsequent structure-activity studies suggested that the potency of BACs as Dhcr7 inhibitors decrease with the length of their hydrocarbon chain: C10>C12>>C14>C16. Real-time qPCR analysis revealed upregulation of the genes related to cholesterol biosynthesis and downregulation of the genes related to cholesterol efflux, suggesting a feedback response to the inhibition. Furthermore, an oxidative metabolite of 7-DHC that was previously identified as a biomarker *in vivo* was also found in cells exposed to BACs by liquid chromatography-mass spectrometry.”³⁸

“We performed a high-throughput screen of 1,600 antiseptics, additives, and drugs, and found that, of the numerous structural classes of compounds included in the screen, the QUATS were the most mitochondrially toxic class, both in terms of inhibition of ATP synthesis and mitochondrial O₂ consumption. QUATS have the structure of lipophilic cations, which are known to be preferentially taken up by mitochondria (Murphy and Smith 2007). In summary, our findings suggest that the QUATS CPC and BAK, which are used as disinfectants in consumer products, inhibit mitochondrial complex 1 and show antiestrogenic activity *in vitro* at low (micromolar) concentrations that may be physiologically relevant. We hypothesize a mechanistic relationship between these outcomes, where by the antiestrogenic activity of these compounds is mediated by mitochondrial inhibition.”³⁹

“QAC cytotoxicity to MDCK II cells *in vitro* is initiated by mitochondrial dysfunction at sub-lethal concentrations, followed by mitochondrial fragmentation and decreased cellular energy charge at slightly higher concentrations. In isolated mitochondria all of the QAC tested were shown to act via a common mechanism involving inhibition of NADH ubiquinone oxidoreductase (complex I) and of mitochondrial ADP-phosphorylation. QAC-induced mitochondrial dysfunction results in apoptosis (concentrations ≤ LD90), followed by a shift to necrotic cell death at concentrations above LD90.”⁴⁰

“This study tested whether QAC concentrations could be detected in the blood of 43 random volunteers, and whether QAC concentrations were associated with markers of inflammation, mitochondrial function,

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	and cholesterol synthesis in a dose dependent manner. QAC concentrations were detected in 80% of study participants, and were associated with decreased mitochondrial function and an increase in inflammatory cytokines in a dose dependent manner. Cholesterol synthesis pathway intermediaries were generally increased, indicating disruption in cholesterol homeostasis. This is the first study to demonstrate that chronic exposure to QACs results in measurable concentrations in human blood, and to also demonstrate significant correlations between QAC level and meaningful biomarkers related to health.” ⁴¹
<i>Metabolites</i>	
<i>Synergistic or Antagonistic Effects</i>	
Environmental and Human Health Exposure and Risk Values	
<i>RfC/RfD</i>	
<i>ATSDR-MRL</i>	
<i>Adverse Effect Levels: DNEL, PNEC, PNEI</i>	
Health Based Exposure Limits	
<i>NIOSH-REL/IDLH/Ceiling Limits</i>	
<i>OSHA-PEL</i>	
<i>ACGIH TLV-TWA</i>	
<i>TLV-STEL</i>	
<i>Biomonitoring Action Limits</i>	
<i>Drinking Water Standards</i>	
<i>Other</i>	<p>Since the 2006 RED, 2237 individual human health incidents have been reported for ADBAC in OPP’s Incident Data System (IDS) from September 1, 2006 to March 3, 2017. The largest number of incidents (814) occurred when handling liquid concentrate products, followed by ready to use (RTU) spray products (337), RTU trigger sprayer products (244), and RTU wipes (235).</p> <p>A few incidents are summarized below:</p> <ul style="list-style-type: none"> • A maintenance worker at a gas station used an ADBAC/DDAC disinfectant product. Another worker there was allegedly exposed to it and developed respiratory distress and ultimately died. She had previously had chronic obstructive pulmonary disease. • An airline employee developed respiratory distress resulting in death. Chemical exposure to an ADBAC/DDAC product and other three [sic] cleaning products was the potential cause. No other details were provided. • A two year old asthmatic child who used a breathing machine died

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	<p>after removing an ADBAC RTU household cleaning and disinfectant product from an unlocked cabinet and spilling it on toys.</p> <ul style="list-style-type: none"> • A 34 year old diabetic resident of a nursing home had a heart attack and later died at the hospital. A partially used can of ADBAC foam product was found in her room. The director of nursing indicated that this patient had previously used this product to clean her room without incident. • A 68 year dementia patient in a nursing home ingested an ABDAC/DDAC [sic] disinfectant product that was being used to clean wheelchairs during the overnight shift.⁴² <p>“The case is described of a 44 year old pharmacist who developed severe occupational asthma threatening his continued employment, confirmed by serial measurement of peak expiratory flow at home and work. The cause was found to be the cleaning agent used in his office when it was unoccupied. Bronchial challenge testing identified the specific agent to which he was sensitized as lauryl dimethyl benzyl ammonium chloride, a constituent of the floor cleaner. Substitution of this floor cleaner by a simple detergent cleaner led to a substantial improvement in his asthma, confirmed by repeated serial peak flow measurements.”⁴³</p> <p>“Alkyl (C12-16) Dimethylbenzylammonium Chloride was assigned a Benchmark Score of 1 based on criteria 1c. very high persistence combined with very high aquatic toxicity and very high toxicity for Group II Human endpoints (acute toxicity, skin irritation, and eye irritation). It may be noted that fewer data gaps would not impact this Benchmark score.”⁴⁴</p>
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
PBT	
<i>Persistence</i>	<p>“We have determined the occurrence of 19 QACs 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 (n = 40; median of 58.9 µg/g). The total QAC concentrations in these samples were significantly higher than in samples collected before the COVID-19 pandemic (p < 0.05; n = 21; median of 36.3 µg/g). Higher QAC concentrations were found in households that generally disinfected more frequently (p < 0.05). Disinfecting products commonly used in these homes were analyzed, and the QAC profiles in dust and in products were similar,</p>

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	suggesting that these products can be a significant source of QACs. Our findings indicate that indoor exposure to QACs is widespread and has increased during the pandemic.” ⁴⁵
<i>Bioaccumulation</i>	
<i>BAF</i>	
<i>BCF</i>	The whole body BCF in fish was estimated to be 79. ² “There is potential for acute exposure to aquatic organisms in the water column because of the high solubility of ADBAC in water... However, bioconcentration in aquatic organisms is not expected despite the high log K _{ow} of 3.91 (>3) because ADBAC is highly soluble in water and, being a positively-charged compound, is tightly sorbed to soil and sediment, which are typically negatively-charged.” ³
<i>BMF</i>	
<i>Ecological Toxicity</i>	ADBACs have a strong tendency to bind to sediment/soil (K _{ads} >5000, K _{oc} >600,000) and chronic exposure to benthic invertebrates is expected. One chronic sediment toxicity study is available for the midge: 80% ai; 28-d NOAEC - 520 mg/kg sediment; 28-d LOAEC - 1200 mg/kg sediment; 14-d LC50 = 548 mg/kg sediment. Chronic studies also are anticipated to be required for a freshwater amphipod and an estuarine/marine amphipod. ³ Additional testing anticipated to be required for aquatic plant toxicity and pollinators (honeybees). ³
<i>Aquatic Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</i>	On an acute exposure basis, ADBAC is highly toxic to freshwater and marine/estuarine fish and freshwater invertebrates. Freshwater invertebrates are especially sensitive to ABDAC on an acute exposure basis, as the acute toxicity classification for ABDAC is very highly toxic. Freshwater fish LC₅₀ = 280 ug ai/L; NOAEC = 32.2 ug ai/L Estuarine/marine fish LC₅₀ = 310 ug ai/L Freshwater invertebrates EC₅₀ = 5.9 ug ai/L; NOAEC = 4.15 ug ai/L ^{3,20} Exposures to benzalkonium chloride or benzethonium chloride at concentration ranges (0.05 - 5 mg/L) resulted in toxicity effects to zebrafish embryos and in germline toxicity in <i>C. elegans</i> . These effects included delayed hatching, embryonic mortality, morphological malformations, and neurotoxicity. BAC was the most toxic, with acute lethal toxicity occurring at environmentally relevant concentrations (hundreds of mg/L), which is comparable to other banned chemicals including triclocarban and triclosan. ⁴⁶
<i>Mammalian Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</i>	ADBAC is categorized as slightly toxic to mammals on an acute basis (LD₅₀ = 430 mg/kg-bw) and a chronic NOAEC of 44 mg/kg/day was

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	established. ⁴
<i>Wildlife Toxicity: LC₅₀, EC₅₀, ErC₅₀, NOAEC/NOEC</i>	The results of the dietary avian studies categorized ADBAC as moderately toxic to birds on an acute basis (LC₅₀ = 136 mg/kg-bw), with no chronic data available. ⁴
<i>Breakdown/degradation /combustion products</i>	
<i>Anaerobic degradation</i>	“There is uncertainty about whether sorption or biodegradation of ADBAC would predominate during wastewater treatment. In the absence of data on the extent for ADBAC to sorb to sludge biomass during wastewater treatment, data from an Activated Sludge Sorption Isotherm (ASSI) study are needed.” ³
<i>Aerobic degradation</i>	“Based on a biodegradation study, ADBAC readily degrades into 60% carbon dioxide in 13 days. ADBAC is immobile in soil. The available soil mobility study shows that ADBAC has a strong tendency to bind to sediment/soil with Freundlich Kads values range from 5,123 to 32,429 depending on the soil type where as the corresponding Koc values range from 640,389 to 6,171,657 depending on the soil type. Due to its strong adsorption to soils, ADBAC is not expected to contaminate surface and ground waters.” ⁴
<i>Other observable ecological effects (e.g. BOD)</i>	
<i>Fate and Transport: Aquatic</i>	<p>Quaternary ammonium compounds have been detected worldwide in domestic wastewater, sludge, treated effluent, surface water, and sediment. It is anticipated that the majority of QAC applications leads to their eventual release into sewers and WWTPs. These compounds have been detected in aquatic environments, and at higher concentrations in locations downstream of the discharge of municipal WWTP effluents, hospitals, and industrial effluents (Hora, 2020).</p> <p>A solid phase extraction method was developed and used for determination of Benzalkonium chloride (BAC - CAS 8001-54-5) in the environment. “Concentration levels of BAC - ranging from 1.2 to 36.6 micrograms per liter - were found in [untreated wastewater and] surface-water samples collected downstream from different wastewater treatment discharges, thus indicating its input and persistence through the wastewater-treatment process.” Note: for untreated wastewater, sample results for combined C₁₂BAC and C₁₄BAC varied from 12 µg/L to 42 µg/L, while stream surface water samples</p>

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	<p>varied from below the detection limit (5 out of 7 locations) to 3.7 µg/L.⁴⁷</p> <p>Presence in surface water and sediments upstream and downstream of WWTPs in Austria: Σ C12-C18 BAC: Surface water ranges from 0.04 - 2.61 µg/L; sediment ranges from 7 - 5840 µg/kg dm</p> <p>Samples downstream of WWTP often were less than samples taken upstream - both for surface water and sediment, so presence was not heavily impacted by WWTP discharge. Study also sampled waste water from different businesses; hospitals and laundries had the highest values for C10-C18 DDAC (max 176 µg/L) and C12-C18 BAC (max 3929 µg/L)⁴⁸</p> <p>“Concentration in effluents varied over a large range. A majority of the “high concentration” effluents showed, even after ten times dilution, concentrations of ATACs and/or BACs that could pose a risk to the aquatic environment. Ecotoxicological data is lacking especially for long chained ATACs. All the selected compounds were present in all sludges. Concentrations in sludge varied much less than in effluents. Patterns of individual compound concentrations were not clearly different among countries.”⁴⁹</p>
<i>Fate and Transport: Terrestrial</i>	
<i>Fate and Transport: Atmospheric</i>	
<i>Transport Issues</i>	<p>“ADBAC is completely soluble in water, and based on its low vapor pressure and Henry’s Law value, is not expected to partition from soil and water into air. ADBAC is stable to hydrolysis at pH values of 5, 7, and 9 (MRID 40835602), with half-lives ranging from 150 to 379 days, and stable to photodegradation in pH 7 buffered aqueous solutions, but degraded in water in the presence of a photosensitizer with a half-life of 7 days (MRID 40835603)”³</p>
<i>Factors affecting bioavailability</i>	
Global Environmental Impacts	
<i>Ozone Depletion Potential (ODP)</i>	
<i>Global Climate Change</i>	
<i>Greenhouse Gas Production</i>	
<i>Acid Rain Formation</i>	
Special Reports	
<i>EU/Other Countries</i>	<p>EU Hazard Classification & labeling: <i>Danger!</i> According to the classification provided by companies to ECHA in CLP notifications this</p>

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	substance is toxic if swallowed, causes severe skin burns and eye damage, is very toxic to aquatic life, is toxic in contact with skin, is very toxic to aquatic life with long lasting effects and causes serious eye damage. ²
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Number of EPA Registered Products that contain ADBAC – 2017 FWP

PC code	CAS Number	Ingredient Name	Number of active AD registrations as of 8/25/16 ¹	Number of active RD registrations as of 8/25/16 ¹
069104	53516-76-0	Alkyl (60% C ₁₄ , 30% C ₁₆ , 5% C ₁₈ , 5% C ₁₂) dimethyl benzyl ammonium chloride	271	2
069105	68424-85-1	Alkyl (50% C ₁₄ , 40% C ₁₂ , 10% C ₁₆) dimethyl benzyl ammonium chloride	329	1
069106	8001-54-5	Alkyl (50% C ₁₂ , 30% C ₁₄ , 17% C ₁₆ , 3% C ₁₈) dimethyl benzyl ammonium chloride	2	0
069107	139-08-2	Alkyl (100% C ₁₄) dimethyl benzyl ammonium chloride	4	0
069111	8045-21-4	Alkyl (50% C ₁₂ , 30% C ₁₄ , 17% C ₁₆ , 3% C ₁₈) dimethyl ethylbenzyl ammonium chloride	13	0
069119	73049-75-9	Dialkyl (60% C ₁₄ , 30% C ₁₆ , 5% C ₁₈ , 5% C ₁₂) methyl benzyl ammonium chloride	37	0
069122	121-54-0	Benzenemethanaminium, N,N-dimethyl-N-(2-(2-(4-(1,1,3,3-tetramethylbutyl)phenoxy)ethoxy)ethyl)-, chloride	11	0
069125	1330-85-4	Dodecylbenzyl trimethyl ammonium chloride	1	0
069137	68424-85-1	Alkyl (60% C ₁₄ , 25% C ₁₂ , 15% C ₁₆) dimethyl benzyl ammonium chloride	9	0
069140	61789-71-7	Alkyl (61% C ₁₂ , 23% C ₁₄ , 11% C ₁₆ , 2.5% C ₁₈ , 2.5% C ₁₀ , trace C ₈) dimethyl benzyl ammonium chloride	1	0
069141	68424-85-1	Alkyl (58% C ₁₄ , 28% C ₁₆ , 14% C ₁₂) dimethyl benzyl ammonium chloride	23	0
069154	85409-23-0	Alkyl (68% C ₁₂ , 32% C ₁₄) dimethyl ethylbenzyl ammonium chloride	203	2
069167	68956-79-6	Alkyl (60% C ₁₄ , 30% C ₁₆ , 5% C ₁₂ , 5% C ₁₈) dimethyl ethylbenzyl ammonium chloride	2	0
069171	68989-01-5	Alkyl (50% C ₁₄ , 40% C ₁₂ , 10% C ₁₆) dimethyl benzyl ammonium saccharinate	7	0
069175	68391-01-5	Alkyl (67% C ₁₂ , 25% C ₁₄ , 7% C ₁₆ , 1% C ₁₈) dimethyl benzyl ammonium chloride	29	0
069184	68424-85-1	Alkyl (95% C ₁₄ , 3% C ₁₂ , 2% C ₁₆) dimethyl benzyl ammonium chloride	16	0
069195	68391-01-5	Alkyl (41% C ₁₄ , 28% C ₁₂ , 19% C ₁₈ , 12% C ₁₆) dimethyl benzyl ammonium chloride	1	0
128928	63449-41-2	Alkyl (67% C ₁₂ , 25% C ₁₄ , 7% C ₁₆ , 1% C ₈ , C ₁₀ , and C ₁₈) dimethyl benzyl ammonium chloride	7	0

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129012	61789-18-2	Alkyl (as in fatty acids of coconut oil) trimethyl ammonium chloride	1	0
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¹ Toxplanet Chemical Identity page for Alkyl dimethylbenzyl ammonium chloride: <https://chemical-search.toxplanet.com/#/product-search/chem-id/ei-fts-search/2813d580-b882-466f-9b5b-36d2c5a3d526>

² European Chemicals Agency (ECHA) Substance Infocard for Quaternary ammonium compounds, benzyl-C12-16-alkyldimethyl, chlorides accessed at: <https://echa.europa.eu/substance-information/-/substanceinfo/100.063.913>

³ United States Environmental Protection Agency (2017) Alkyls Dimethyl Benzyl Ammonium Chloride (ADBAC) Final Work Plan, Registration Review: Initial Docket, Case Number 03050, Docket Number EPA-HQ-OPP-2015-0737. See Appendix C for additional ecotoxicity results.

⁴ United States Environmental Protection Agency (2006) Prevention, Pesticides and Toxic Substances; Reregistration Eligibility Decision for Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) EPA's Pesticide Docket EPA-HQ-OPP-2006-0339

⁵ Hora, Priya, et al. (2020) Increased Use of Quaternary Ammonium Compounds during the SARS-CoV-2 Pandemic and Beyond: Consideration of Environmental Implications. *Environmental Science and Technology*

⁶ United States Environmental Protection Agency (2008), Office of Pollution Prevention and Toxics, Screening-Level Hazard Characterization of High Production Volume Chemicals; Fatty Nitrogen Derived Cationics

⁷ Herron, J. M.; Hines, K. M.; Tomita, H.; Seguin, R. P.; Cui, J. Y.; Xu, L., Multi-omics investigation reveals benzalkonium chloride disinfectants alter sterol and lipid homeostasis in the mouse neonatal brain. *Toxicol. Sci.* **2019**, *171*, 32-45.

⁸ Herron, J.; Reese, R. C.; Tallman, K. A.; Narayanaswamy, R.; Porter, N. A.; Xu, L., Identification of environmental quaternary ammonium compounds as direct inhibitors of cholesterol biosynthesis. *Toxicol. Sci.* **2016**, *151*, 261-270.

⁹ Melin, V. E., Potineni, H., Hunt, P., Griswold, J., Siems, B., Werre, S. R., & Hrubec, T. C. (2014). Exposure to common quaternary ammonium disinfectants decreases fertility in mice. *Reproductive Toxicology*, *50*, 163–170. <https://doi-org.umasslowell.idm.oclc.org/10.1016/j.reprotox.2014.07.071>

¹⁰ Melin VE, Melin TE, Dessify BJ, Nguyen CT, Shea CS, Hrubec TC. Quaternary ammonium disinfectants cause subfertility in mice by targeting both male and female reproductive processes. *Reprod Toxicol.* 2016 Jan;59:159-66. doi: 10.1016/j.reprotox.2015.10.006. Epub **2015** Nov 12. PMID: 26582257.

¹¹ Hrubec TC, Melin VE, Shea CS, et al. Ambient and Dosed Exposure to Quaternary Ammonium Disinfectants Causes Neural Tube Defects in Rodents. *Birth Defects Res.* 2017;109(14):1166-1178. doi:10.1002/bdr2.1064

¹² Hostetler 2018. Letter to the Editor in *Birth Defects Research*, Comments on "Ambient and Dosed Exposure to Quaternary Ammonium Disinfectants Causes Neural Tube Defects in Rodents." Accessed at: <https://onlinelibrary.wiley.com/doi/full/10.1002/bdr2.1194>

¹³ Buttar HS. Embryotoxicity of benzalkonium chloride in vaginally treated rats. *J Appl Toxicol.* 1985 Dec;5(6):398-401. doi: 10.1002/jat.2550050612. PMID: 4078221.

¹⁴ Potential Designated Chemicals: Quaternary Ammonium Compounds, March 4, 2020; Office of Environmental Health Hazard Assessment (OEHA) Scientific Guidance Panel (SGP) for Biomonitoring California, Page 11. Accessed 2/9/2021: <https://biomonitoring.ca.gov/sites/default/files/downloads/PotenDesigQACs030420.pdf>

Updated EHS Summary of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) for the MA TURA Science Advisory Board Meeting – March 11, 2021

- ¹⁵ Hostetler K., Fisher L., Burruss B., Submitted for Publication Prenatal Developmental Toxicity of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) and Didecyl Dimethyl Ammonium Chloride (DDAC) in CD Rats and New Zealand White Rabbits. Toxicology Regulatory Services, Charlottesville, VA, USA
- ¹⁶ Ferk F, Misík M, Hoelzl C, Uhl M, Fuerhacker M, Grillitsch B, Parzefall W, Nersesyan A, Micieta K, Grummt T, Ehrlich V, Knasmüller S. Benzalkonium chloride (BAC) and dimethyldioctadecyl-ammonium bromide (DDAB), two common quaternary ammonium compounds, cause genotoxic effects in mammalian and plant cells at environmentally relevant concentrations. *Mutagenesis*. 2007 Nov;22(6):363-70. doi: 10.1093/mutage/gem027. Epub 2007 Jul 26. PMID: 17656635.
- ¹⁷ Melin, V. E., Melin, T. E., Dessify, B. J., Nguyen, C. T., Shea, C. S., & Hrubec, T. C. (2016). Quaternary ammonium disinfectants cause subfertility in mice by targeting both male and female reproductive processes. *Reproductive Toxicology (Elmsford, N.Y.)*, 59, 159–166. <https://doi-org.umasslowell.idm.oclc.org/10.1016/j.reprotox.2015.10.006>
- ¹⁸ Directive 98/8/EC concerning the placing biocidal products on the market; Inclusion of active substances in Annex I to Directive 98/8/EC: Assessment Report. Alkyl (C12-16) dimethylbenzyl ammonium chloride. Product-type 8 (wood preservative). Page 46. June 2015. <https://echa.europa.eu/documents/10162/b9030b10-c8af-211b-456a-4f4b11d509b7>
- ¹⁹ European Union, Biocidal Products Committee (BPC); Opinion on the application for approval of the active substance: Alkyl (C₁₂₋₁₆) dimethylbenzyl ammonium chloride; Product type: 3. ECHA/BPC/267/2020
- ²⁰ Larsen, S., Hansen, R., Hammer, M., Tegner, U. Poulsen, O., Nielsen, G. (2004) Adjuvant effect of quaternary ammonium compounds in a murine model, Department of Chemical Working Environment, National Institute of Occupational Health, *S.T. Larsen et al. / Toxicology Letters 151 (2004) 389–398* doi:10.1016/j.toxlet.2004.03.008
- ²¹ Xue Y, Hieda Y, Kimura K, Takayama K, Fujihara J, Tsujino Y. Kinetic characteristics and toxic effects of benzalkonium chloride following intravascular and oral administration in rats. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2004 Nov 5;811(1):53-8. doi: 10.1016/j.jchromb.2004.03.075. PMID: 15458722.
- ²² Wentworth AB, Yiannias JA, Davis MD, Killian JM. Benzalkonium Chloride: A Known Irritant and Novel Allergen. *Dermatitis*. 2016 Jan-Feb;27(1):14-20. doi: 10.1097/DER.000000000000160. PMID: 26756511.
- ²³ Uter W, Lessmann H, Geier J, Schnuch A. Is the irritant benzalkonium chloride a contact allergen? A contribution to the ongoing debate from a clinical perspective. *Contact Dermatitis*. 2008 Jun;58(6):359-63. doi: 10.1111/j.1600-0536.2008.01327.x. PMID: 18503686.
- ²⁴ ECHA REACH database, accessed at <https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13152/7/4>
- ²⁵ Chiambaretta F, Pouliquen P, Rigal D. Allergie et conservateurs. A propos de trois cas d'allergie au chlorure de benzalkonium [Allergy and preservatives. A Chiambaretta F, Pouliquen P, Rigal D. Allergie et conservateurs. A propos de trois cas d'allergie au chlorure de benzalkonium [Allergy and preservatives. Apropos of 3 cases of allergy to benzalkonium chloride]. *J Fr Ophtalmol*. 1997;20(1):8-16. French. PMID: 9099278. propos of 3 cases of allergy to benzalkonium chloride]. *J Fr Ophtalmol*. 1997;20(1):8-16. French. PMID: 9099278.
- ²⁶ Association of Occupational and Environmental Clinics (AOEC) Exposure code lookup for Alkyl Dimethylbenzyl ammonium chloride (CAS #: 68424-85-1) accessed on 10/14/20: <http://www.aoecdata.org/ExpCodeLookup.aspx>
- ²⁷ Gonzalez M, Jégu J, Kopferschmitt MC, Donnay C, Hedelin G, Matzinger F, Velten M, Guilloux L, Cantineau A, de Blay F. Asthma among workers in healthcare settings: role of disinfection with quaternary ammonium compounds. *Clin Exp Allergy*. 2014 Mar;44(3):393-406. doi: 10.1111/cea.12215. PMID: 24128009.
- ²⁸ Purohit et al (2000) Quaternary ammonium compounds and occupational asthma. *Int Arch Occup Environ Health* 73: 423-427

Updated EHS Summary of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) for the MA TURA Science Advisory Board Meeting – March 11, 2021

- ²⁹ Bernstein, Jonathan, et al (1994) A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines. *Journal of Allergy and Clinical Immunology*
- ³⁰ Asmus, S. et al (1999). Bronchoconstrictor additives in bronchodilator solutions. *Journal of Allergy and Clinical Immunology*.
- ³¹ Vandenplas, O., D'Alpaos, V., Evrard, G., Jamart, J., Thimpont, J., Huaux, F., Renauld, J., (2013) Asthma related to cleaning agents: a clinical insight. *British Medical Journal* (<http://dx.doi.org/10.1136/bmjopen-2013-003568>)
- ³² Kwon, D.; Kwon, J.-T.; Lim, Y.-M.; Shim, I.; Kim, E.; Lee, D.-H.; Yoon, B.-I.; Kim, P.; Kim, H.-M., Inhalation toxicity of benzalkonium chloride and triethylene glycol mixture in rats. *Toxicol. Appl. Pharmacol.* **2019**, *378*, 114609.
- ³³ Dumas O, Varraso R, Boggs KM, et al. Association of Occupational Exposure to Disinfectants With Incidence of Chronic Obstructive Pulmonary Disease Among US Female Nurses. *JAMA Netw Open.* 2019;2(10):e1913563. doi:10.1001/jamanetworkopen.2019.13563
- ³⁴ Dumas O, Boggs KM, Quinot C, Varraso R, Zock JP, Henneberger PK, Speizer FE, Le Moual N, Camargo CA Jr. Occupational exposure to disinfectants and asthma incidence in U.S. nurses: A prospective cohort study. *Am J Ind Med.* 2020 Jan;63(1):44-50. doi: 10.1002/ajim.23067. Epub 2019 Nov 6. PMID: 31692020; PMCID: PMC6891131.
- ³⁵ Preller L, Doekes G, Heederik D, Vermeulen R, Vogelzang PF, Boleij JS. Disinfectant use as a risk factor for atopic sensitization and symptoms consistent with asthma: an epidemiological study. *Eur Respir J.* 1996 Jul;9(7):1407-13. doi: 10.1183/09031936.96.09071407. PMID: 8836651.
- ³⁶ Quirce S, Barranco P. Cleaning agents and asthma. *J Investig Allergol Clin Immunol.* 2010;20(7):542-50; quiz 2p following 550. PMID: 21313993.
- ³⁷ Larsen ST, Verder H, Nielsen GD. Airway effects of inhaled quaternary ammonium compounds in mice. *Basic Clin Pharmacol Toxicol.* 2012 Jun;110(6):537-43. doi: 10.1111/j.1742-7843.2011.00851.x. Epub 2012 Jan 18. PMID: 22188809.
- ³⁸ Herron, J.; Reese, R. C.; Tallman, K. A.; Narayanaswamy, R.; Porter, N. A.; Xu, L., Identification of environmental quaternary ammonium compounds as direct inhibitors of cholesterol biosynthesis. *Toxicol. Sci.* **2016**, *151*, 261-270.
- ³⁹ Datta, S.; He, G.; Tomilov, A.; Sahdeo, S.; Denison, M. S.; Cortopassi, G., In vitro evaluation of mitochondrial function and estrogen signaling in cell lines exposed to the antiseptic cetylpyridinium chloride. *Environ. Health Perspect.* **2017**, *125*, 087015-087015.
- ⁴⁰ Inácio, Â. S.; Costa, G. N.; Domingues, N. S.; Santos, M. S.; Moreno, A. J. M.; Vaz, W. L. C.; Vieira, O. V., Mitochondrial dysfunction is the focus of quaternary ammonium surfactant toxicity to mammalian epithelial cells. *Antimicrob. Agents Chemother.* **2013**, *57*, 2631-2639
- ⁴¹ Hrubec TC, et al. (2020) PREPRINT Altered Toxicological Endpoints in Humans with Quaternary Ammonium Compound Exposure doi: <https://doi.org/10.1101/2020.07.15.20154963>
- ⁴² USEPA/Office of Pesticide Programs; Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC), Final Work Plan, Registration Review: Initial Docket Case Number 0305, March 2017. Docket Number EPA-HQ-OPP-2015-0737
- ⁴³ Burge PS, Richardson MN. Occupational asthma due to indirect exposure to lauryl dimethyl benzyl ammonium chloride used in a floor cleaner. *Thorax.* 1994 Aug;49(8):842-3. doi: 10.1136/thx.49.8.842. PMID: 8091336; PMCID: PMC475138.
- ⁴⁴ GreenScreen for Safer Chemicals - Alkyl (C12-16) Dimethylbenzylammonium Chloride (CAS # 68424-85-1) (2014) Clean Production Action, NSF International
- ⁴⁵ Guomao Zheng, Gabriel M. Filippelli, and Amina Salamova Increased Indoor Exposure to Commonly Used Disinfectant during the COVID-19 Pandemic, *Environmental Science & Technology Letters* **2020** 7 (10), 760-765 DOI: 10.1021/acs.estlett.0c00587

Updated EHS Summary of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) for the MA TURA Science Advisory Board Meeting – March 11, 2021

⁴⁶ Sreevidya VS, Lenz KA, Svoboda KR, Ma H. Benzalkonium chloride, benzethonium chloride, and chloroxylenol - Three replacement antimicrobials are more toxic than triclosan and triclocarban in two model organisms. *Environ Pollut.* 2018 Apr;235:814-824. doi: 10.1016/j.envpol.2017.12.108. Epub 2018 Feb 21. PMID: 29348075.

⁴⁷ Ferrer I, Furlong ET. Identification of alkyl dimethylbenzylammonium surfactants in water samples by solid-phase extraction followed by ion trap LC/MS and LC/MS/MS. *Environ Sci Technol.* 2001 Jun 15;35(12):2583-8. doi: 10.1021/es001742v. PMID: 11432568.

⁴⁸ Norbert Kreuzinger, Maria Fuerhacker, Sigrid Scharf, Maria Uhl, Oliver Gans, Britta Grillitsch, Methodological approach towards the environmental significance of uncharacterized substances — quaternary ammonium compounds as an example, Volume 215, Issues 1–3, 2007, Pages 209-222, ISSN 0011-9164, <https://doi.org/10.1016/j.desal.2006.10.036>.

⁴⁹ Kaj L, Wallberg P, Brorström-Lundén E (2014) Quaternary ammonium compounds: analyses in a Nordic cooperation on screening. Nordisk Ministerraðd <https://norden.diva-portal.org/smash/get/diva2:760465/FULLTEXT01.pdf>